Synthesis of a Library of Antiviral Silvestrol Analogues and Development of Novel Methodologies in the Field of Radical Chemistry

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Ich hab ‘ne gute Nachricht und ‘ne schlechte auch
Zuerst die schlechte: Wir zerfall’n zu Staub
Wir werden zu Asche, kehren in das Nichts […]
Und jetzt die gute: Heute nicht

– *Danger Dan*

Kurzzusammenfassung

Synthese einer Bibliothek antiviraler Silvestrol-Analoga und Entwicklung neuer Methoden in der Radikalchemie

Göran Schulz

Schlagwörter: Totalsynthese, Medizinalchemie, Rocaglate, Flavagline, Silvestrol, antivirale Wirkstoffe, eIF4A Inhibitor, Radikalchemie, Decarboxylierung, Iodazid, Bromazid, C-H-Aktivierung.

Der erste Teil der vorliegenden Dissertation beschäftigt sich mit dem Design und der Synthese von Silvestrol- und Rocaglamid-Derivaten mit antiviralen Eigenschaften. Die beiden Naturstoffe, die zur Gruppe der Flavagline gehören, wurden aus unterschiedlichen Arten der Gattung *Aglaia* isoliert. Durch ihre Wirkung als selektive Translationshemmer fanden sie in bisherigen medizinalchemischen Arbeiten vor allem als Leitstrukturen in der Krebsforschung Anwendung. Später wurde jedoch auch eine antivirale Wirkung gegen eine Vielzahl von RNA-Viren nachgewiesen. In der vorliegenden Dissertation wurden auf der Grundlage früherer Arbeiten mehrere Strategien für die totalsynthetische Herstellung dieser Klasse von Naturstoffen ausgearbeitet. Dies ermöglichte die Synthese einer Bibliothek von insgesamt 40 Derivaten. Durch die biologischen Testungen von 27 dieser Verbindungen gegen Hepatitis E, die von Kooperationspartnern der Ruhr-Universität Bochum durchgeführt wurden, konnten sowohl neue Struktur-Aktivitäts-Zusammenhänge aufgeklärt werden als auch bestätigt werden, dass die aus der Krebsforschung bekannten Zusammenhänge ebenfalls auf die antiviralen Eigenschaften anwendbar sind. Gleichzeitig konnten Kandidaten identifiziert werden, die sowohl eine höhere antivirale Aktivität als auch eine im Verhältnis geringere Zytotoxizität als beide Naturstoffe aufweisen.

Der zweite Teil dieser Dissertation beschäftigt sich mit der Entwicklung neuartiger synthetischer Methoden im Bereich der Radikalchemie. Basierend auf einer Decarboxylierung vom MINISCI-Typ konnte ein Zugang zu den synthetisch nützlichen Alkoxyaminen gefunden werden. Durch Anwendung innerhalb einer Synthese zum (±)-Indatralin konnte die synthetische Relevanz der Methode gezeigt werden. Die Studien zur Reaktivität eines polymergebundenen Diazidiodiat(I)-Komplexes, der das hochexplosive Iodazid in kontrollierter Weise freisetzt, ermöglichten die Aufklärung gleich mehrerer bisher noch nicht beschriebener radikalischer Mechanismen. Zusätzlich wurden mehrere Methoden entwickelt, um Bromazid aus stabilen Vorläufermolekülen in situ zu generieren und in organischen Lösungsmitteln für die 1,2-Funktionalisierung von Alkenen und die chemoselektive Oxidation von sekundären Alkoholen zu nutzen.

Abstract

Synthesis of a Library of Antiviral Silvestrol Analogues and Development of Novel Methodologies in the Field of Radical Chemistry

Göran Schulz

Keywords: Total synthesis, medicinal chemistry, rocaglates, flavaglines, silvestrol, antiviral drugs, eIF4A inhibitor, radical chemistry, decarboxylation, iodine azide, bromine azide, C-H activation.

The first part of this dissertation deals with the design and synthesis of silvestrol and rocaglamide derivatives exhibiting antiviral properties. These two natural products, which belong to the Flavagline group, were isolated from different species of the genus *Aglaia*. Due to their activity as selective translation inhibitors, they found application in previous medicinal chemistry research primarily as lead structures in cancer research, but later antiviral activity against a variety of RNA viruses was also demonstrated. In the present dissertation, several strategies for the total synthesis of this class of natural products were elaborated on the basis of previous work. This allowed the preparation of a library of 40 derivatives in total. The biological testing of 27 of these compounds against hepatitis E, which was carried out by collaborators at the Ruhr University Bochum, revealed new structure-activity relationships and confirmed that the correlations established in cancer research are also applicable to the antiviral properties. In addition, it was possible to identify candidates that exhibited both higher antiviral activity and proportionally lower cytotoxicity than both natural products.

The second part of this dissertation deals with the development of novel synthetic methodologies in the field of radical chemistry. Based on a MINISCI-type decarboxylation, an access to synthetically useful alkoxyamines was established. The relevance of this method was demonstrated by its application in the context of a new total synthesis approach for (±)-indatraline. Studies on the reactivity of a polymer-bound bis(azido)iodiate(I) complex, which releases the highly explosive iodine azide in a controlled manner, enabled the elucidation of several previously unknown radical mechanisms. Furthermore, several methods have been developed to generate bromine azide from stable precursors *in situ* for the use in organic solvents to accomplish 1,2-functionalization of alkenes and chemoselective oxidation of secondary alcohols.

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Abbreviations

4-DMAP	4-dimethylaminopyridine
Ac	acetyl
ADME	absorption, distribution, metabolism and excretion
AIBN	2,2′-azobis(2-methylpropionitrile)
Ala	alanine
AMP	adenosine monophosphate
AMPPNP	adenosine 5′-(β,γ-imido)triphosphate
Ar	aryl
Asp	aspartic acid
ATP	adenosine triphosphate
Bn	benzyl
bp	boiling point
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
CoA	coenzyme A
CSA	camphorsulfonic acid
CXCR4	C-X-C chemokine receptor type 4
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron donating group
ee	enantiomeric excess
EI	electron ionization
eIF	eukaryotic initiation factor

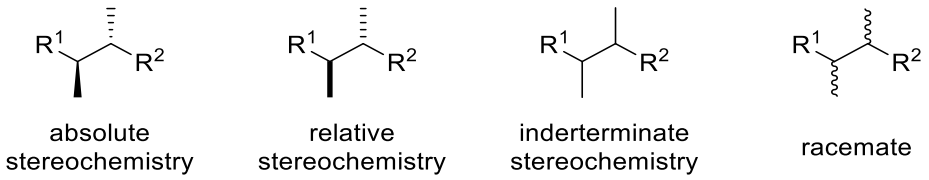
EPR	electron paramagnetic resonance spectroscopy
Et	ethyl
ESI	electrospray ionization
ESIPT	excited-state intramolecular proton transfer
EWG	electron withdrawing group
FDA	U.S. Food and Drug Administration
Glu	glutamic acid
gp120	human immunodeficiency virus envelope glycoprotein gp120
h	hours
HEV	hepatitis E virus
HMDS	hexamethyldisilazide
HIV	human immunodeficiency virus
HOBt	hydroxybenzotriazole
HPAD	hydroxyphenyl acetate decarboxylase
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
pK_a	negative base-10 logarithm of the acid dissociation constant
^{i}Pr	*iso*-propyl
IAD	indole acetate decarboxylase
IR	infrared spectroscopy
IRES	internal ribosomal entry site
$\mathcal{J}$	coupling constant (NMR)
LC	liquid chromatography
LED	light-emitting diode
Me	methyl
min	minutes
MOM	methoxymethyl
mp	melting point
Ms	mesyl (methanesulfonyl)
MS	mass spectroscopy
MTBE	methyl *tert*-butyl ether
myc	MYC gene

NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Nf	nonaflyl (1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl)
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
PAD	phenyl acetate decarboxylase
Ph	phenyl
PIC	preinitiation complex
PP_i	pyrophosphate
PROXYL	2,2,5,5-tetramethyl-1-pyrrolidinyloxy
Py	pyridine
rac	racemic
RdRp	RNA-dependent RNA polymerase
RNA	ribonucleic acid
RocA	rocaglamide
rt	room temperature
SAR	structure-activity relationship
sat.	saturated
SET	single-electron transfer
t	time
T	temperature
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFDO	methyl(trifluoromethyl)dioxirane
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography

TMS	trimetylsilyl
t_R	retention time
Ts	tosyl (*p*-toluenesulfonyl)
tub	tubulin gene
UTR	untranslated region
UV	ultraviolet

Preliminary Remarks

Stereochemistry is represented in this work as follows: Wedged bonds represent absolute stereochemistry, while bars indicate relative stereochemistry. In addition, single bonds refer to undefined stereochemistry and wavy bonds are used for racemic mixtures.



Parts of the research of this work have already been published:

[1] T. Kösel*, G. Schulz*, G. Dräger, A. Kirschning, *Angew. Chem. Int. Ed.* **2020**, *59*, 12376-12380.
Photochemical Transformations with Iodine Azide after Release from an Ion-Exchange Resin

[2] G. Schulz, A. Kirschning, *Org. Biomol. Chem.* **2021**, *19*, 273-278.
Metal free decarboxylative aminoxylation of carboxylic acids using a biphasic solvent system

[3] G. Schulz*, C. Victoria*, A. Kirschning., E. Steinmann, *Nat. Prod. Rep.* **2021**, *38*, 18-23.
Rocaglamide and silvestrol: A long story from anti-tumor to anti-coronavirus compounds

[4] G. Schulz*, V. George*, D. Taser*, A. Kirschning, *J. Org. Chem.* **2023**, *88*, 3781-3786.
Taming Bromine Azide for Use in Organic Solvents—Radical Bromoazidations and Alcohol Oxidations

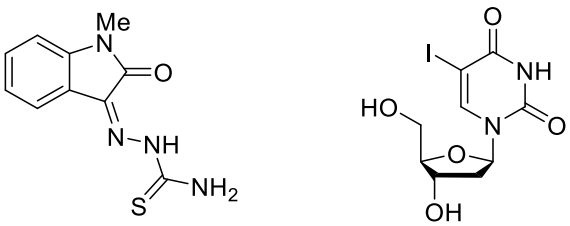
Topic A: Synthesis of a Library of Antiviral Silvestrol Analogues

A1 Introduction

A1.1 Drug-based Strategies for Combating Viral Infections

In the history of humankind, viruses have often been the cause of pandemics that have claimed millions of lives worldwide. Currently, the global COVID-19 pandemic, in which the number of cases and deaths continues to rise,[1] reminds us that the development of new antiviral substances is becoming increasingly urgent.[2] Although some viral diseases such as polio or smallpox have been nearly eradicated by vaccination, others, particularly the human immunodeficiency virus and the hepatitis C virus, have not yet been combated by the vaccine approach.[3] Nevertheless, even with vaccines in hand, these remain only a preventive measure. Antiviral drugs that combat the virus during an acute infection, rather than just relieving symptoms, are only available against a limited number of viruses. The main reason for this is that viruses are obligate intracellular parasites whose replication entirely relies on the intracellular resources of their host cell. Therefore, it is challenging to identify virus-specific metabolic processes as appropriate targets for antiviral therapy.[4]

In contrast to antibiotic research, the era of antiviral chemotherapy did not begin until the 1950s with the observation that thiosemicarbazones, originally used to treat tuberculosis, were also effective against vaccinia and poxviruses.[5] This led to the development of methisazone (**1**, Figure 1), which became the first synthetic antiviral agent to be successfully tested in a human in 1962.[6] One year later, idoxuridine (**2**, Figure 1), a uridine analogue synthesized in 1959 with the intention of developing an anticancer drug,[7] was approved by the FDA for the treatment of herpes simplex keratitis.[8]



methisazone (**1**) idoxuridine (**2**)

Figure 1 Structures of the first synthetic antiviral drugs methisazone (**1**) and idoxuridine (**2**).

Since then, more than 100 different antiviral drugs have been approved with activity against ten different viruses, including HIV, hepatitis B and C, as well as herpes, influenza and, most recently, SARS-CoV-2.[9] About 90% of these compounds have been approved within the last 30 years, as previously new candidates could only be identified via classical trial and error methods. It was not until the 1980s, particularly with the need to combat HIV, that a better understanding of viral life cycles led to the discovery and validation of several targets for therapeutic intervention.[3]

In contrast to mammalian cells, bacteria or fungi, viruses as a group do not share the same genome type or replication principle. Viral genomes can consist of single- or double-stranded DNA or RNA. These contain all the information required for replication and protein biosynthesis taking place in the host cell. Outside the host cells, viruses appear as virions (Figure 2 shows the virion of an RNA virus), which have a shell of viral proteins, the capsid, to protect the genetic material. In addition, the capsid may be surrounded by a lipid membrane called the viral envelope.[4]

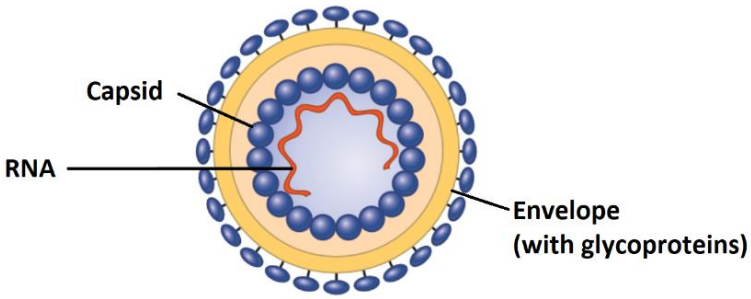
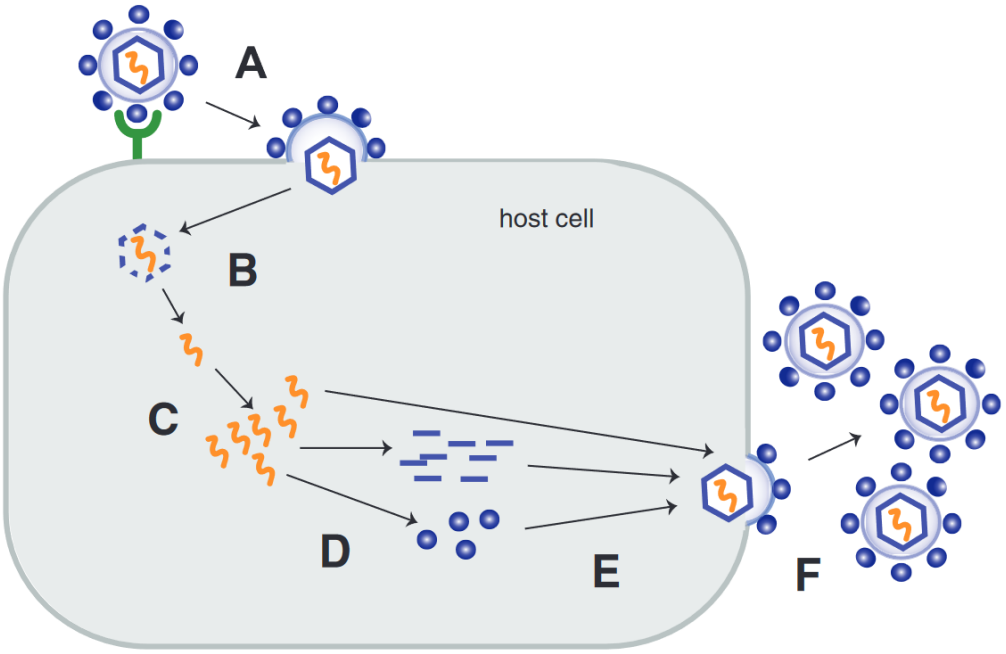


Figure 2 Schematic representation of an enveloped single-stranded RNA virus.[10]

The replicative cycle differs greatly between virus species, but some fundamental stages are similar among all of them (Scheme 1). First, the glycoproteins on the surface of the virion are attached to specific receptors of the cell. The virus particle then enters the cell by fusion with the plasma membrane or by endocytosis. The uncoating process leads to the release of the viral genome and capsid proteins into the cytoplasm.[10] The subsequent mechanisms for replication of the viral genome as well as protein synthesis vary, depending on the genome type and the location of virus replication in the cell. While many viruses bring their own DNA or RNA polymerases encoded on their genome,[11] transcription, post-transcriptional modifications and translation of viral mRNA rely on cellular mechanisms in most cases.[4] The newly formed genomes and envelope proteins are transported to a specific collection site where they self-assemble into new virus particles. These particles are then released either by cell lysis (in the case of most non-enveloped viruses) or by budding from the cell membrane, resulting in the formation of a lipid envelope (in the case of enveloped viruses). In some cases, such as HIV, an additional step called maturation is required to generate the infectious virion from the initial non-infectious assembly product.[12]



Scheme 1 Basic stages of viral replication: (a) binding, (b) entry, (c) genome replication, (d) gene expression, (e) assembly and (f) release.[4]

Antiviral drug candidates should interfere with and inhibit one of these steps by targeting either viral or host cell proteins. The first approach is likely to yield more specific, less toxic compounds with a narrow spectrum of antiviral activity and a higher likelihood of resistance development. The second approach could deliver antiviral compounds with a broader spectrum of activity and a lower risk of resistance development, but a higher probability of toxicity. The strategy of choice depends on the characteristics of the virus and the targets offered by the virus and the host cell. Consequently, it is not surprising that there are examples of approved antiviral drugs for both approaches.[3]
In the case of HIV, for instance, the binding of the virions can be inhibited by anionic polymers such as polyvinylalcohol sulfate (**3**, Figure 3). The negatively charged polymer interacts with the positively charged amino acids of the HIV glycoprotein gp120, preventing it from binding to heparan sulfate, the primary binding site on the cell surface.[3,13] Alternatively, the virus-cell fusion can be inhibited by targeting receptors on the cell surface. For example, plerixafor (**4**) acts as an antagonist for the chemokine receptor CXCR4, resulting in inhibition of HIV viral particle entry into T cells.[14]

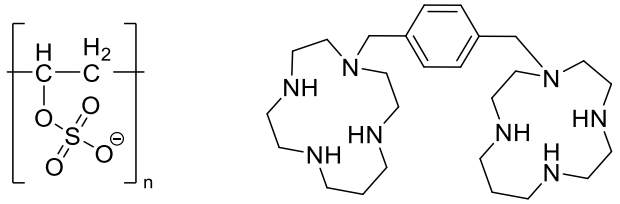


Figure 3 Virus adsorption inhibitor polyvinylalcohol sulfate (**3**) and virus–cell fusion inhibitor plerixafor (**4**).

Another frequently addressed target are the DNA and/or RNA polymerases. Remdesivir (**5**, Figure 4) is a prodrug of the adenosine analogue GS-441524 (**6**), which after phosphorylation competes with the natural substrate ATP (**7**) for the viral RNA-dependent RNA polymerase (RdRp).[15] Steric hindrance of the nitrile moiety causes delayed chain termination when a certain number of additional bases are added to the growing RNA strand (three bases for SARS-CoV-2 RdRp[16], five for Ebola virus RdRp[17]).

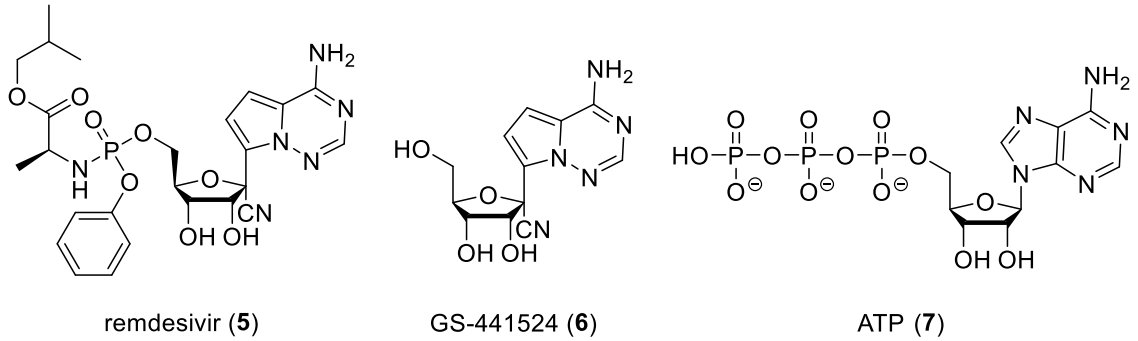
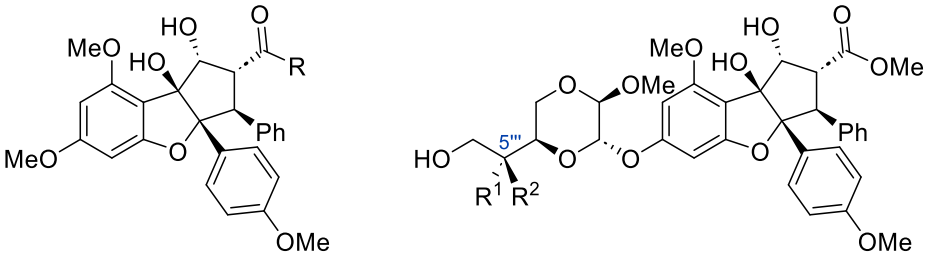


Figure 4 The broad-spectrum antiviral drug remdesivir (**5**) is a prodrug of GS-441524 (**6**), which, in its triphosphorylated form, is an analogue of adenosine triphosphate (ATP, **7**).

In addition to the compounds presented here, other antiviral chemotherapeutics have been developed that target the uncoating, protein biosynthesis, assembly, viral release and other processes specific to certain viruses.[4]

A1.2 History of Flavaglines

Flavaglines are a class of natural products that originate from several species of *Aglaia* (Meliaceae), a genus of trees that grow in subtropical and tropical forests of Southeast Asia, Northern Australia and the Pacific region.[18] Their history began in 1975 with the analysis of alcoholic extracts of *Aglaia elliptifolia* showing significant activity against P-388 lymphatic leukemia in CDF_1 mice and inhibitory activity *in vitro* against cells derived of human epidermoid carcinoma of the nasopharynx (KB cells).[19] Seven years later, the authors of this initial study succeeded in isolating and structurally elucidating the substances responsible for the biological activity. The first members of the flavaglines were named rocagloic acid (**8**, Figure 5) and rocaglamide (**9**).[20] In 1990, total synthesis by TROST and co-workers confirmed the absolute configuration of rocaglamide (**9**).[21]



R = OH, rocagloic acid (**8**)
R = NMe_2, rocaglamide (**9**)

R^1 = OH, R^2 = H silvestrol (**10**)
R^1 = H, R^2 = OH *epi*-silvestrol (**11**)

Figure 5 Structures of rocagloic acid (**8**), rocaglamide (**9**), and silvestrol (**10**) and its 5'''-epimer *epi*-silvestrol (**11**).

To date, over 100 additional flavaglines have been isolated from various species of the genus *Aglaia* and tested for their biological properties.[22] In addition to anti-cancer activity, insecticidal,[23] anti-fungal[24] and anti-inflammatory properties[25] have also been demonstrated.

Special attention was attracted by silvestrol (**10**) and its 5'''-epimer *epi*-silvestrol (**11**), which were isolated for the first time from *Aglaia foveolata* in 2004.[26] Structurally, these compounds are most interesting due the unusual dioxanyloxy moiety attached to the phenyl ring A. Both epimers are more cytotoxic in *in vitro* tests against breast (MCF-7, ED_{50} = 1.5 nM for **10**; 5.5 nM for **11**), prostate (LNCaP, ED_{50} = 1.5 nM for **10**; 3 nM for **11**), lung (Lu1, ED_{50} = 1.2 nM for **10**; 3.8 nM for **11**) and colon (HT-29, ED_{50} = 0.7 nM for **10**; 2.29 mM for **11**) cancer cell lines than rocaglamide (**9**, ED_{50} = 5.0 nM against HT-29) and other analogues that lack the dioxanyloxy moiety.[26,27,28]

Although antiviral activity of extracts from *Aglaia roxburghiana* var. *beddomei* was described as early as 1983,[29] it was not until 2008 that an antiviral activity of flavaglines was proven for the first time. In a study describing the cytotoxic activities of newly discovered flavaglines isolated from *Aglaia foveolata*, the authors found that desacetylpyramidaglain C (**12**, Figure 6) exhibited moderate antiviral activity against herpes simplex virus type 1 (HSV-1). Remarkably, this plant metabolite also showed moderate antibacterial activity against *Mycobacterium tuberculosis* H37Ra.[28,30]

With the opening of this new therapeutic door, the focus of flavagline has shifted from anticancer to antiviral leads. In 2017 and 2018, GRÜNWELLER and co-workers reported on the inhibition of hepatitis E, corona, zika and picornavirus replication by silvestrol (**10**) without pronounced cytotoxic effects for primary cell lines (Huh-7 and MRC-5).[31] Several other studies confirmed these results on various RNA viruses *in vivo* and *in vitro*, reporting very low cytotoxicity of silvestrol (**10**) at nanomolar concentrations.[32]

The synthetic rocaglamide derivative (–)-CR-31-B (**13**) also shows antiviral activity against zika, lassa and Crimean-Congo hemorrhagic fever viruses, but lower activity against hepatitis E virus than silvestrol (**10**).[33] Recently, (–)-CR-31-B (**13**) was also reported to inhibit SARS-CoV-2 replication *in vitro* and *in vivo*. Even nanomolar concentrations that did not result in a cytotoxic effect were effective.[34]

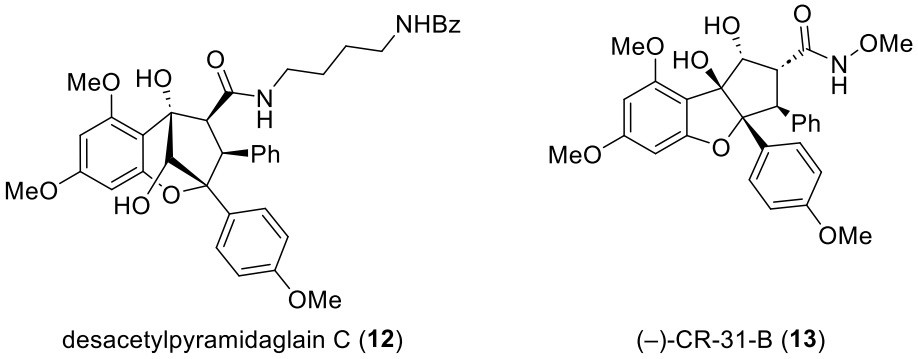
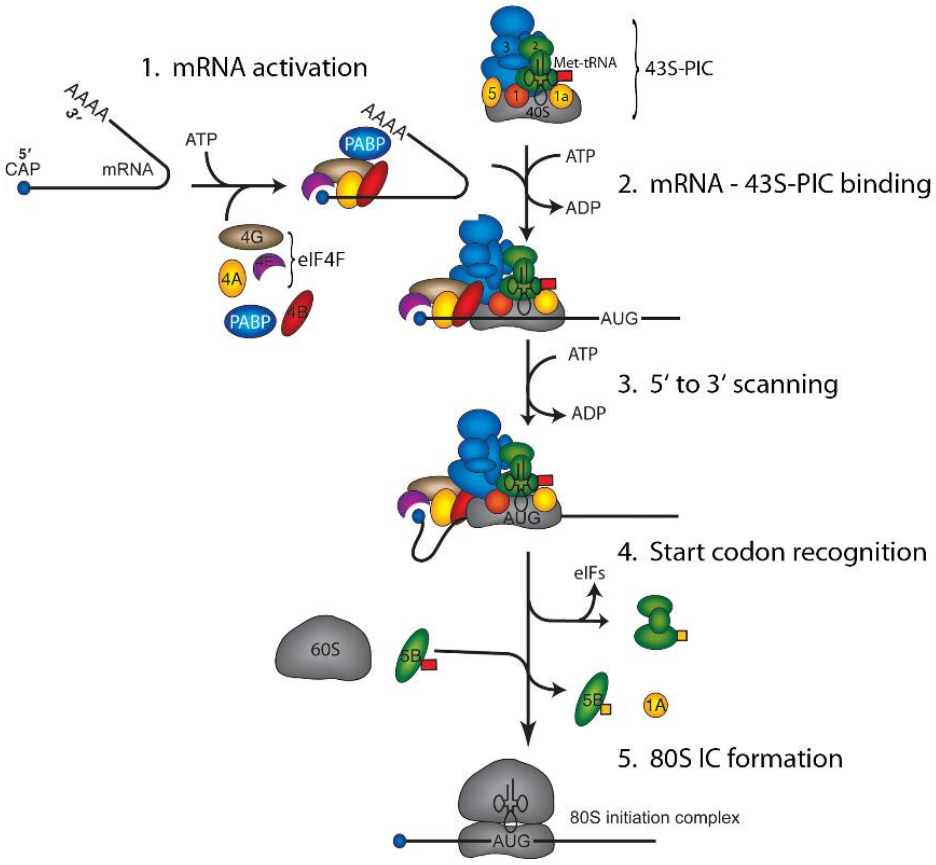


Figure 6 Structures of desacetylpyramidaglain C (**12**) and (–)-CR-31-B (**13**).

A1.3 Mechanism of Action of Flavaglines

As described in Section A1.1, the protein biosynthesis of RNA viruses is mainly dependent on host cell resources. Before the information of the RNA is translated into a protein, initiation processes take place that leads to the binding of the ribosomes to the RNA. In eukaryotes, there are two fundamentally different mechanisms: cap-dependent and cap-independent translation initiation.



Scheme 2 The eukaryotic cap-dependent translation initiation pathway. Initiation factors are shown as circles or complexes, each identified by its number embedded therein.[35]

The first step of cap-dependent translation initiation (illustrated in Scheme 2) is the binding of the 5'-cap of the RNA to the eukaryotic initiation factor 4E (eIF4E). This is a subunit of the heterotrimeric eIF4F complex which also contains the RNA helicase eIF4A and the scaffold protein eIF4G. The helicase eIF4A then unwinds the secondary structure of the mRNA under ATP consumption and removes attached proteins so that the 43S preinitiation complex (43S-PIC) can bind to the 5'-UTR (untranslated region). This complex, accompanied by the protein factors, scans the mRNA chain toward its 3' end to locate the start codon (AUG). After dissociation of the other initiation factors eIF5B mediates the joining of the 60S subunit to form the 80S initiation complex (IC).[36]

In cap-independent initiation processes, either the RNA binds to the translation initiation factors independently of the 5'-cap structure or a specifically folded section within an RNA, called an internal ribosomal entry site (IRES), mediates direct binding to the 40s ribosome.[37] IRES-driven translation has been found primarily in viral RNA, such as poliovirus, rhinovirus, hepatitis A virus and hepatitis C virus.[38]

Flavaglines act by selectively inhibiting the DEAD-box helicase eIF4A of the cap-dependent translation. The abbreviation DEAD stands for the amino acid sequence Asp-Glu-Ala-Asp (D-E-A-D), which is the signature motif of this protein family. The ATP-dependent eIF4A unwinds the secondary structure of the 5'-UTR of mRNA to prepare it for ribosomal binding and subsequent translation. To initiate this process the enzyme first bent the RNA, whereby a bimolecular cavity is formed between the *N*-terminus of eIF4A and two RNA bases.[39] In 2019, IWASAKI *et al.* resolved a crystal structure of a rocaglamide (**9**, RocA)-eIF4A1-polypurine RNA-AMPPNP complex which revealed that flavaglines bind in this cavity (Figure 7).[40] This stabilizes the complex, which blocks 43S scanning and leads to premature initiation of translation, resulting in reduced translation of polypurine-rich RNA in a sequence-selective manner.[41]

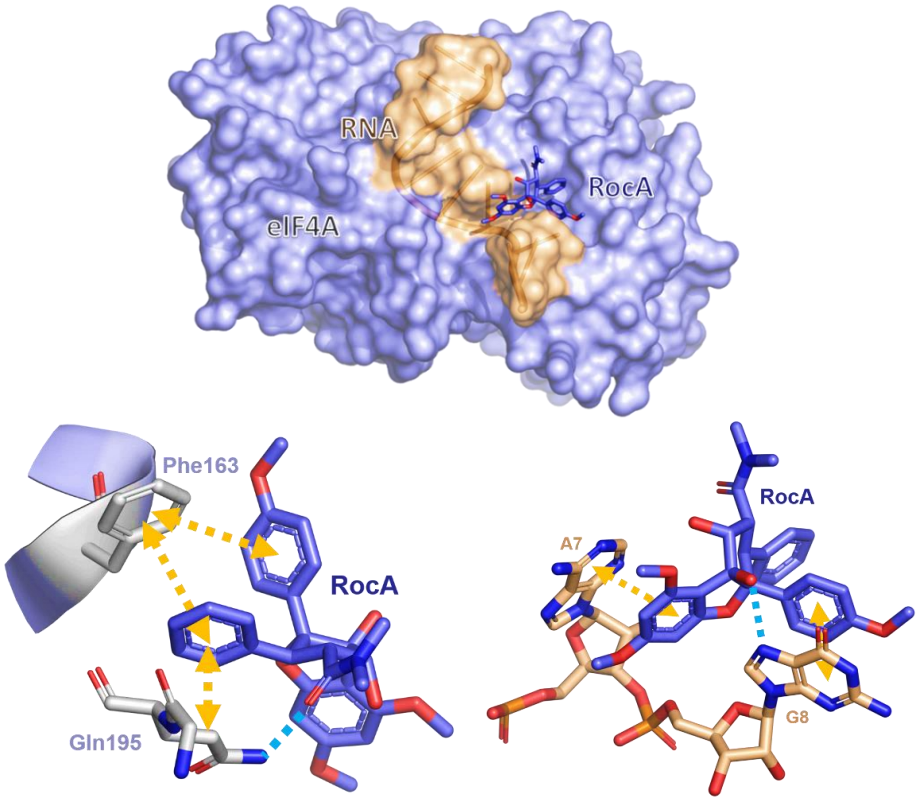


Figure 7 a. Crystal structure of a RocA-eIF4A1-polypurine RNA-AMPPNP complex; **b.** Major interactions along the rocaglamide (**9**)-binding pocket with the RNA (left) and eIF4A (right).[40,42]

The ternary complex is stabilized by multiple interactions (Table 1). The A and B rings each interact with a purine base of the RNA (A with A7 and B with G8) via π stacking. The C ring also establishes π-π interactions with the amino acid Phe163 of the protein. In addition, hydrogen bonds exist through the C2 carbonyl group with Asp198 and Gln195 and through the tertiary alcohol with the N7 position of a guanine base of the RNA substrate.[40]

Table 1 Major structural motifs of flavaglines and their interactions with RNA and eIF4A.[33,40]

Structural motif	Interaction with	Interaction type
A ring	purine base A8 (RNA)	π stacking
B ring	purine base G8 (RNA)	π stacking
C ring	Phe163 (eIF4A)	π stacking
8b-OH	N7 of G8 (RNA)	hydrogen bond
C2 carbonyl	Gln195 (eIF4A) Asp198 (eIF4A)	hydrogen bond
C8 dioxanyloxy	Arg110 (eIF4A) Arg282 (eIF4A) Arg331 (eIF4A)	hydrogen bond

Computational modelling revealed that the additional dioxanyloxy moiety present in silvestrol (**10**) interacts with three arginine residues in eIF4A to further stabilize the silvestrol (**10**)-eIF4A-RNA-complex (Figure 8). This allows silvestrol (**10**) to clamp RNA substrates with short hairpin structures, whereas flavaglines lacking such side chains require substrates with unstructured polypurine-rich sequences.[33]

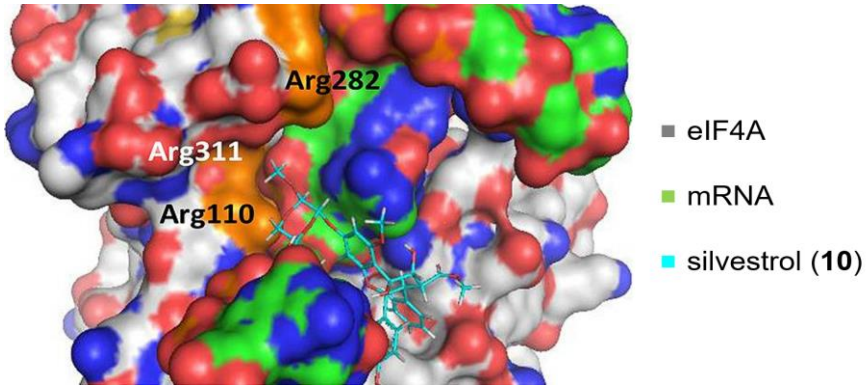


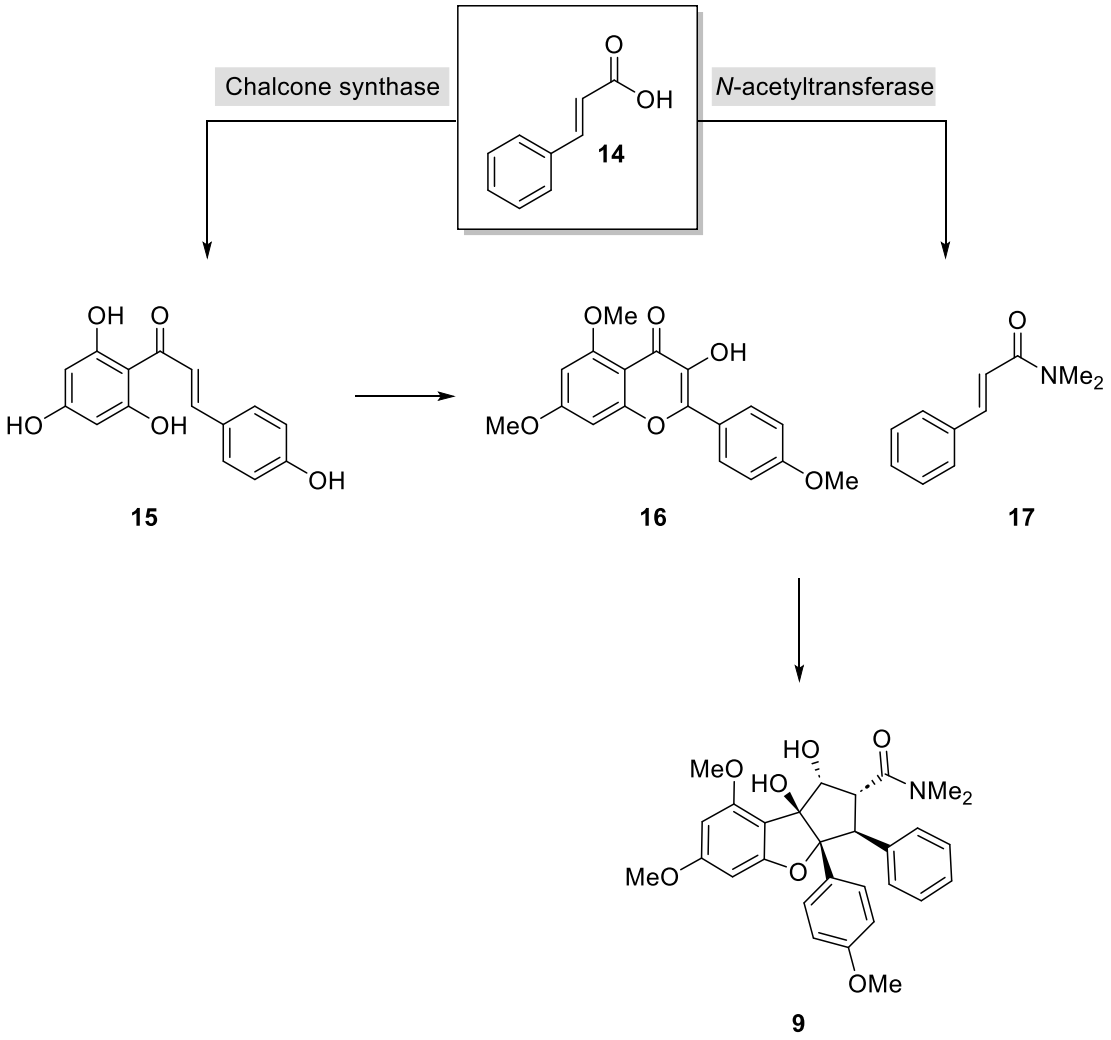
Figure 8 Computational model of the quaternary structure of a silvestrol (**10**)-eIF4A-RNA complex.[33]

The global cellular effect of eIF4A inhibition is limited to around 300 cellular mRNAs which leads to the comparatively low toxicity of flavaglines on primary cells and in animal tests. However, many proto-oncogenic mRNAs with relatively long and structured 5′UTRs are affected, which explains the strong antitumor effect.[43]

Highly structured and polypurine-rich 5'-UTRs are also commonly found in 5'-capped viral RNA, accounting for the antiviral activity of flavaglines. The selective translation inhibition leads to reduced replication of RNA viruses that utilize the hosts protein biosynthesis machinery to replicate.[43]

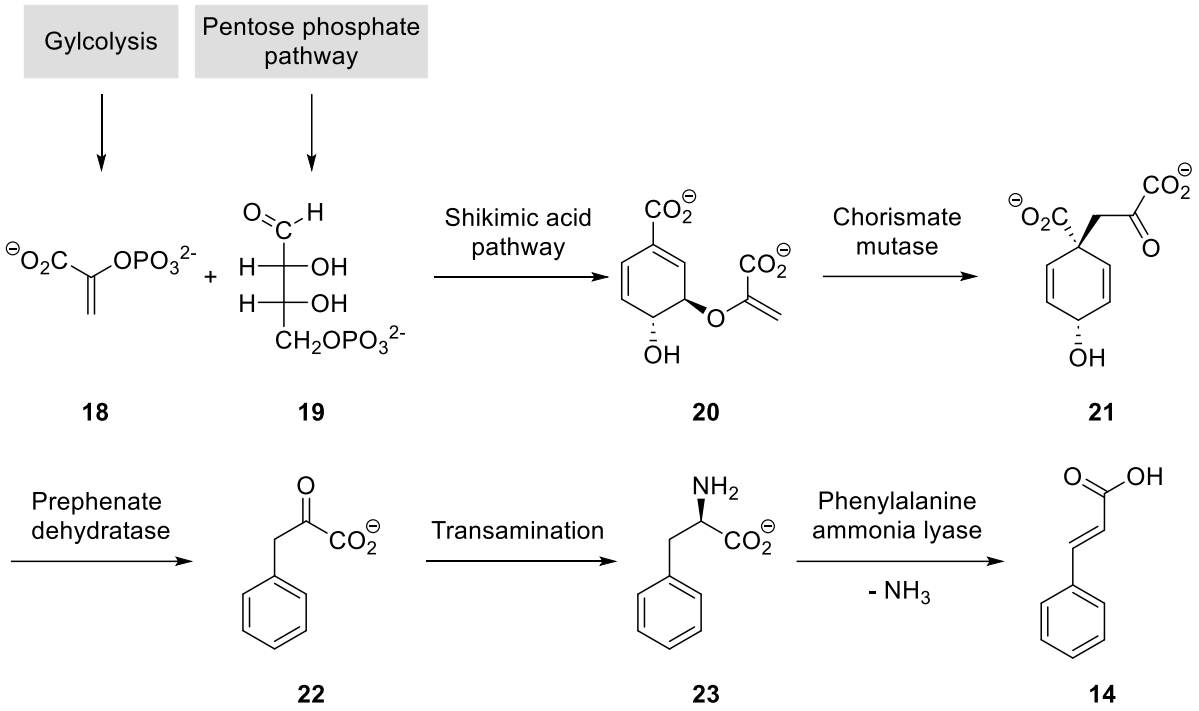
A1.4 Biosynthesis of Flavaglines

The biosynthesis of flavaglines has not yet been exhaustively elucidated. However, this class of secondary metabolites is known to be derived from flavonols and cinnamic acid derivatives, as exemplified by the proposed biosynthetic pathway of rocaglamide (**9**) shown in Scheme 3.[44,45] Chalcone **15**, the precursor of flavonol **16**, is also ultimately based on cinnamic acid (**14**), since cinnamoyl-CoA is the building block for its biosynthesis.[46]



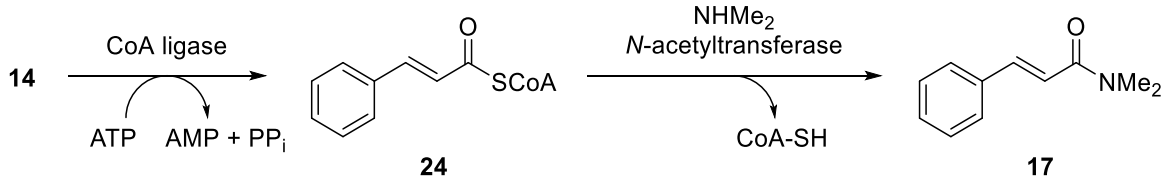
Scheme 3 Proposed biosynthetic pathway of rocaglamide (**9**).[44–46]

As shown in Scheme 4, cinnamic acid (**14**) and its derivatives are derived from the shikimic acid pathway, in which chorismate (**20**) is synthesized from the metabolites phosphoenolpyruvate (**18**, glycolysis) and erythrose-4-phosphate (**19**, pentose phosphate pathway). Chorismate mutase then catalyzes a CLAISEN-type rearrangement leading to the formation of prephenate (**21**). Decarboxylation and rearomatization by prephenate dehydratase give rise to pyruvate (**22**). Finally, cinnamic acid (**24**) is formed by transamination to phenylalanine (**23**) and elimination by phenylalanine ammonia lyase.[47,48]



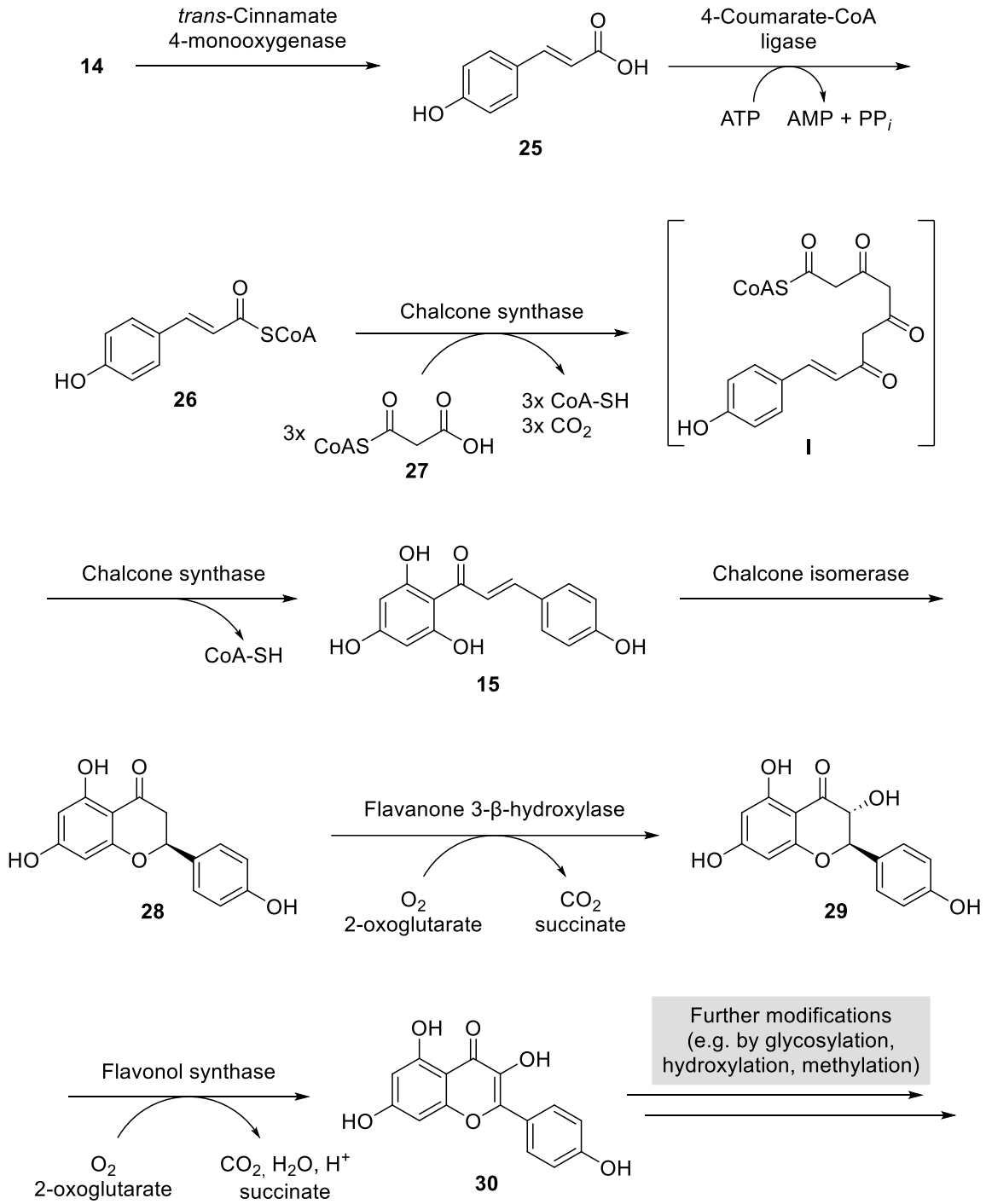
Scheme 4 Biosynthetic pathway of cinnamic acid (**14**).[47,49]

For subsequent functionalization of cinnamic acid (**14**), for example to biosynthesize cinnamic acid amide **17**, conversion to cinnamoyl-CoA (**24**) occurs by a CoA ligase under ATP consumption. The activated thioester can subsequently couple with dimethylamine under mediation by an *N*-acetyltransferase (Scheme 5).[50]



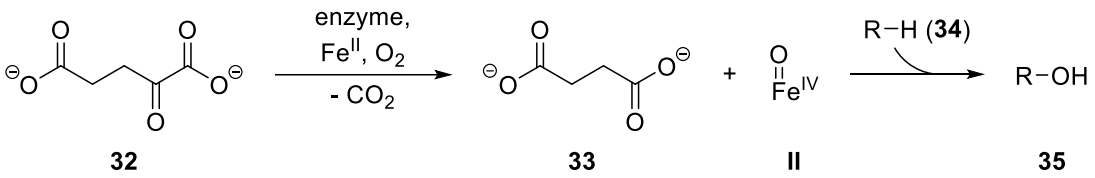
Scheme 5 Biosynthesis of cinnamic acid amide **17** by amidation of cinnamoyl-CoA (**24**).[50,51]

The biosynthesis of flavonols (Scheme 6) begins with selective hydroxylation of cinnamic acid (**14**) by *trans*-cinnamic acid 4-monooxygenase. The starting building block 4-coumaroyl-CoA (**26**) for the chalcone synthase, a type III polyketide synthase, is formed by 4-coumarate-CoA ligase. In an iterative process, three successive decarboxylative condensations with malonyl-CoA (**27**) first form tetraketide intermediate **I**, which subsequently undergoes CLAISEN-type cyclization leading to chalcone **15**.[52] A second cyclization mediated by a chalcone isomerase gives rise to naringenin (**28**) which is then oxidized in a two-step process to kaempferol (**30**).[53,54] Starting from **30**, numerous other flavonols can be derived, e.g. by glycosylation,[55] hydroxylation,[53] and methylation.[56] Thus, kaempferol 5,7,4'-trimethyl ether (**16**), precursor of rocaglamide (**9**), can be formed by *O*-methylation of the three phenolic alcohols.



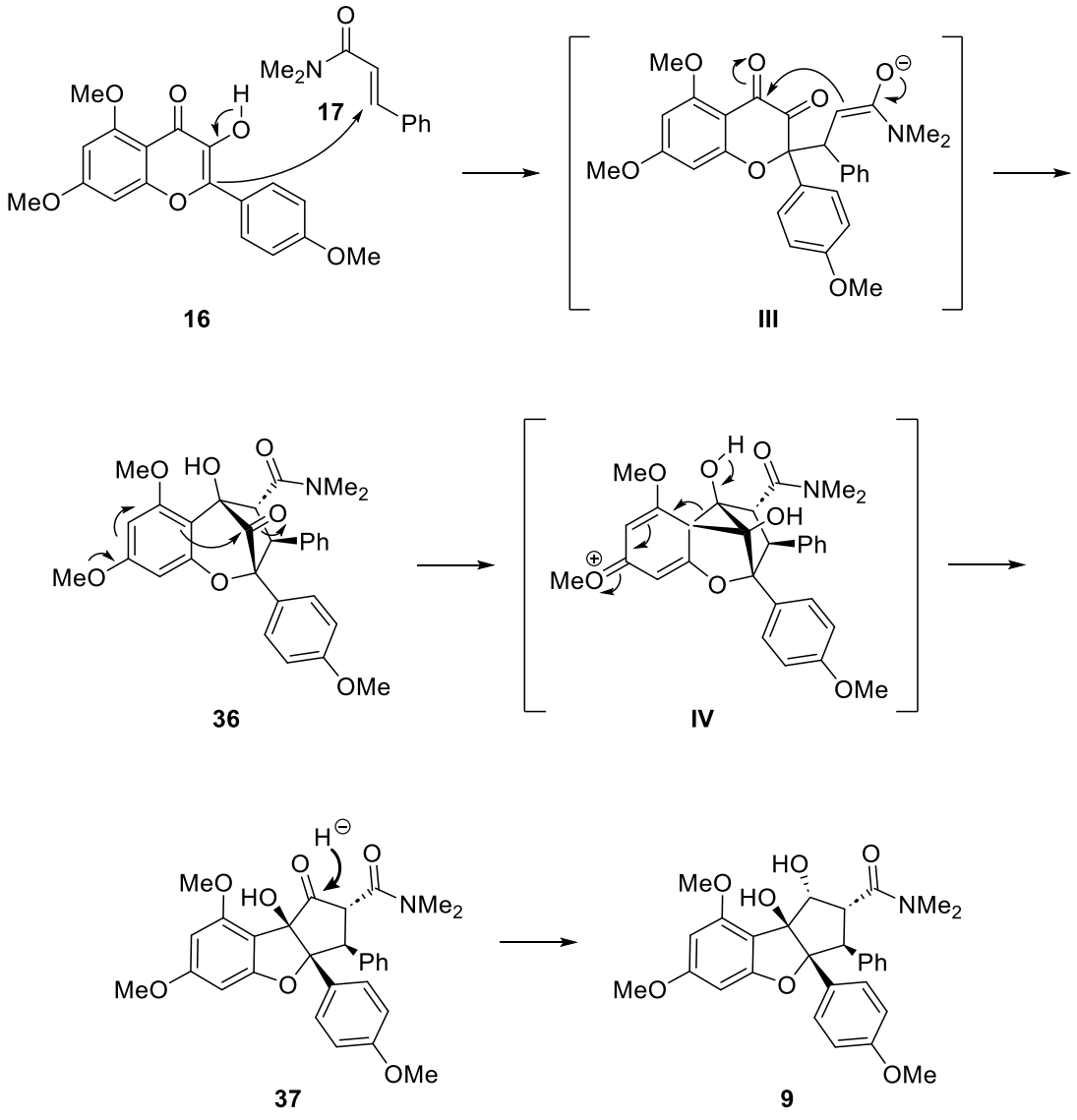
Scheme 6 Biosynthesis of kaempferol (**30**) in plants.[51]

Both enzymes involved in this process, flavone-3ß-hydroxylase and flavonol synthase, belong to the 2-oxogluterate, non-heme-Fe(II)-dependent dioxygenases.[55] Mechanistically, 2-oxoglutaerate (**31**) binds to the active iron site which facilitates oxidative decarboxylation, forming succinate (**32**), CO_2 and iron(IV) intermediate **II**. As illustrated in Scheme 7, active species **II** can subsequently effect hydroxylation or desaturation of substrate **34**.[57]



Scheme 7 General reaction scheme of 2-oxogluterate, non-heme-Fe(II)-dependent dioxygenases.[57]

The enzymes involved in the biosynthetic formation of flavaglines from flavonols and cinnamic acid derivatives are still unknown. However, in 1999 NUGROHO *et al.* proposed a mechanism for the biosynthesis of rocaglamide (**9**) and its derivatives.[44] As shown in Scheme 8, it starts with a MICHAEL-type addition of the flavonol enol to the cinnamic acid derivative **17**. The amide enolate **III** then closes a 5-membered ring by a nucleophilic attack on the carbonyl-C of the flavonol **16**. This forms aglain core **36** which undergoes a α-ketol rearrangement giving rise to cyclopenta[*b*]benzofuran **37**. This rearrangement is mediated by the A ring and can also be described as an electrophilic aromatic *ipso*-substitution in which cyclopropyl **IV** is formed as an intermediate. Finally, ketone **37** is reduced to form rocaglamide (**9**).[44]



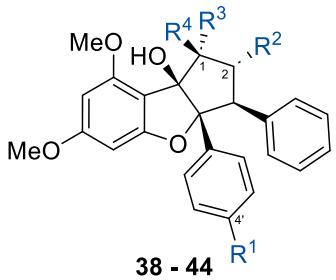
Scheme 8 Proposed biosynthetic origin of rocaglamide (**9**) and other flavaglines.[44]

A1.5 Previous Flavagline-based Medicinal Chemistry Programs

The exceptional biological activity of flavaglines turned this class of natural products into an attractive lead structures for medicinal chemistry programs. Consequently, there is a number of studies published on the development of unnatural flavagline analogues with improved activities and pharmaceutical properties.

Starting from 2009, the research group of DÉSAUBRY reported on the synthesis and biological evaluation of structurally diverse rocaglamide derivatives.[58–61] Thereby, rocaglaol (**38**), a C2 unsubstituted analogue of rocaglamide (**9**), was selected as reference structure. By exchanging of the 4'-methoxy group with a bromide, the cytotoxicity against human cell line KB was significantly improved (Entry 2).[58] The installation of a tertiary, secondary or primary amide at C2 further enhanced the activity (Entries 3 – 5), but also led to an increased sensitivity for multidrug resistance by P-glycoprotein-mediated efflux.[60,61] In order to mimic the H-bond acceptor effect of the amide carbonyl group, a formylation of alcohol OH-1 was approached. This resulted in a slight improvement in activity (Entry 6). Surprisingly, cytotoxicity could be significantly increased by inversion of the configuration of this alcohol and formamidation (Entry 7).[61]

Table 2 Cytotoxicity of flavaglines analogues **38-44** synthesized by the research group of DÉSAUBRY against human cancer cell line from nasopharynx (KB).[58,60,61]



38 - 44

Entry	Compound	R^1	R^2	R^3	R^4	IC_{50} (72 h) / nM		
						[58]	[61]	[60]
1	**38**	OMe	H	OH	H	2	-	-
2	**39**	Br	H	OH	H	<1	15	2.4
3	**40**	Br	$CONMe_2$	OH	H	-	7.5	-
4	**41**	Br	CONHMe	OH	H	-	4.5	-
5	**42**	Br	$CONH_2$	OH	H	-	2	-
6	**43**	Br	H	OCHO	H	-	6.9	-
7	**44**	Br	H	H	NHCHO	-	2.9	1.9

The PORCO group, which has previously accomplished one of the first total syntheses of silvestrol (**10**),[62] reported on their first synthetic rocaglate derivatives in 2012.[63] They hypothesized that a hydroxamate at the C2 would lead to further stabilization of the eIF4A-RNA complex through the formation of hydrogen bonds of the oxygen lone electron pairs. Indeed, they demonstrated that compound (–)-CR-31-B (**13**), an *N*-methoxyamide analogue of rocaglamide (**9**), exerts a similar inhibitory effect on cap-dependent translation as silvestrol (**10**) in human lymphoma BJAB cells (IC_{50} (72 h) ≈ 0.5 nM for both compounds). The drug-like properties of compound **13** such as solubility

and metabolic stability are excellent, whereas permeability is moderate to high. Furthermore, (–)-CR-31-B (**13**) has shown only little toxicity in mice.

More recently, PORCO and co-workers reported on the synthesis of amidino-rocaglate derivatives. This new class of synthetic flavaglines features an imidazoline N-H at C8b, which has a lower pK_a value than the tertiary hydroxyl group of the natural compound. Therefore, it is assumed to act as an enhanced hydrogen bond donor, resulting in improved binding to the RNA.[64] Indeed, a comparison of the inhibitory effect on cap-dependent translation shows that the activity of amidino-rocaglate **45** (Figure 9, IC_{50} = 39 nM) is significantly higher than that of the previous frontrunner (–)-CR-31-B (**13**, IC_{50} = 272 nM). In addition, compound **45** (IC_{50} = 0.97 nM) showed nearly a twofold increase in cytotoxicity against MDA-MB-231 breast cancer cells relative to (–)-CR-31-B (**13**, IC_{50} = 1.9 nM).[64,65]

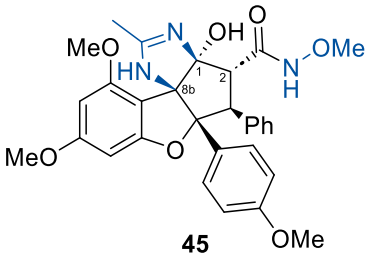
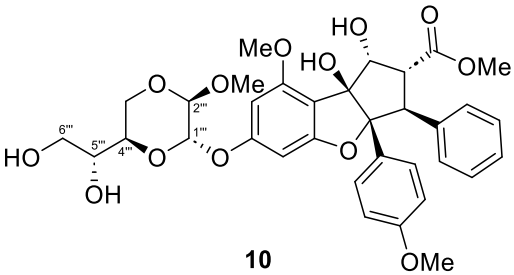
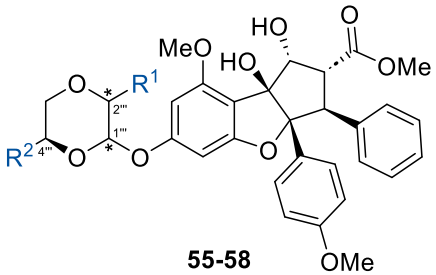


Figure 9 Amidino-rocaglate **45** with imidazoline N-H at C8b position.

The enormous potential of flavaglines as natural product leads for the development of anticancer and antiviral drugs is also proven by the fact that several medicinal chemistry programs have been conducted by the pharmaceutical industry. In 2012, the group of TREMBLAY of INFINITY PHARMACEUTICALS published their work on novel silvestrol (**10**) analogues. In contrast to all previously published work, this involved the design and synthesis of derivatives with modified dioxanyloxy moieties. By testing the inhibitory effect of these compounds on translation of luciferase reporters with highly structured 5'-UTR (myc-LUC) and short 5'-UTR (tub-LUC), they were able to determine the dependence of the activity on the RNA structure (Table 3).

Table 3 Translation initiation inhibitory of silvestrol (**10**) and analogues **55-58** synthesized by the group of TREMBLAY.[66]



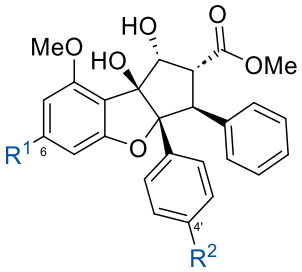


Entry	Compound	R^1	R^2	1'''	EC_{50} (72 h) / nM	
					myc-LUC	tub-LUC
1	**10**	(*R*)-OMe	$HOCH_2$((*R*)-CHOH)	(*S*)	0.8	7
2	**55**	(*R*)-OMe	$HOCH_2CH_2$	(*S*)	1	5
3	**56**	(*R*)-OMe	$HOCH_2$	(*S*)	3	60
4	**57**	(*R*)-OMe	$HOCH_2CH_2$	(*R*)	>200	>3500
5	**58**	(*S*)-OMe	$HOCH_2CH_2$	(*S*)	35	275

Comparison of the effect of the two alcohols at C5''' and C6''' of the dioxanyloxy residue on activity showed that the primary alcohol had a greater impact, as removal of the secondary alcohol did not significantly change the EC_{50} value (Entries 1 – 2). In contrast, shortening the carbon chain by one CH_2 group led to reduced inhibition, especially for RNA with a short 5'-UTR (Entry 3). Furthermore, it was found that the configuration of the stereo centers within the dioxanyloxy ring is critical for the potency of the silvestrol analogues. Both inversion at C1''' or C2''' resulted in a significant loss of activity (Entries 4 – 5).[66]

However, the authors also confirmed that flavaglines substituted by a pseudo-sugar suffer poor ADME properties that preclude their development as a medicine. Therefore, they decided to replace the dioxanyloxy moiety with electron withdrawing substituents (Table 4). Installing a methyl ester (**60**, Entry 3), methyl ketone (**61**, Entry 4), nitrile (**62**, Entry 5) or chlorine (**63,** Entry 6) at C6 led to strong improvements in activity in comparison with methyl rocaglate (**59**). In agreement with the previous work of DÉSAUBRY, the authors found that electron-withdrawing substituents at C4' position increases the translation initiation inhibitory (Entry 7).[66]

Table 4 Translation initiation inhibitory of silvestrol (**10**), methyl rocaglate (**59**) and analogues **60-64** synthesized by the group of TREMBLAY.[66]

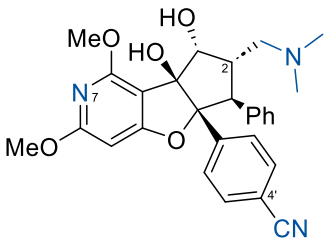


10, 59-64

Entry	Compound	R^1	R^2	EC_{50} (72 h) / nM	
				myc-LUC	tub-LUC
1	**10**	dioxanyloxy	OMe	0.8	7
2	**59**	OMe	OMe	10	90
3	**60**	C(O)OMe	OMe	0.2	4
4	**61**	C(O)Me	OMe	1	30
5	**62**	CN	OMe	0.9	15
6	**63**	Cl	OMe	4	70
7	**64**	OMe	CN	2	17

In 2020, the pharmaceutical company eFFECTOR THERAPEUTICS published on the development of novel synthetic flavaglines with improved drug-like properties. As in the program of INFINITY PHARMACEUTICALS, they substituted the methoxy group at C4' position for a nitrile to increase the activity. In addition, the phenyl A ring was exchanged for a pyridine and the natural dimethyl amide of rocaglamide (**9**) was reduced to dimethylamine. In this way, the frontrunner molecule eFT226 (**65**, Figure 10) was obtained, which exhibits excellent physicochemical properties and significant antitumor activity against MDA-MB-231 breast cancer cell line (IC_{50}(eFT226, **65**) = 10.6 nM, IC_{50}(rocaglamide, **9**) = 20 nM).[67] eFT226 is also the first flavagline tested in clinical trials in humans.

Phase 1/2 trials are currently ongoing for the treatment of selected advanced malignant solid tumors and mild or moderate COVID-19.[68,69] The results of these studies are expected to be released in 2023.



65

Figure 10 Structure of eFT226 (**65**), the first flavagline in clinical trials.[67–69]

In addition to the design of the highlighted frontrunner molecules, the presented studies also contributed to the elucidation of structure-activity relationships. A summary of these results is illustrated in Figure 11. It is evident that the focus of the previous works was primarily on C2, C6 and C4'. Compared to rocaglamide (**9**), a strong improvement in activity was observed by changing the natural substituents at all three positions. In contrast to phenyl rings A and B, ring C was only slightly investigated. All previous attempts only led to a reduction of the biological activity. The same applies for modifications at C8 and C3'.

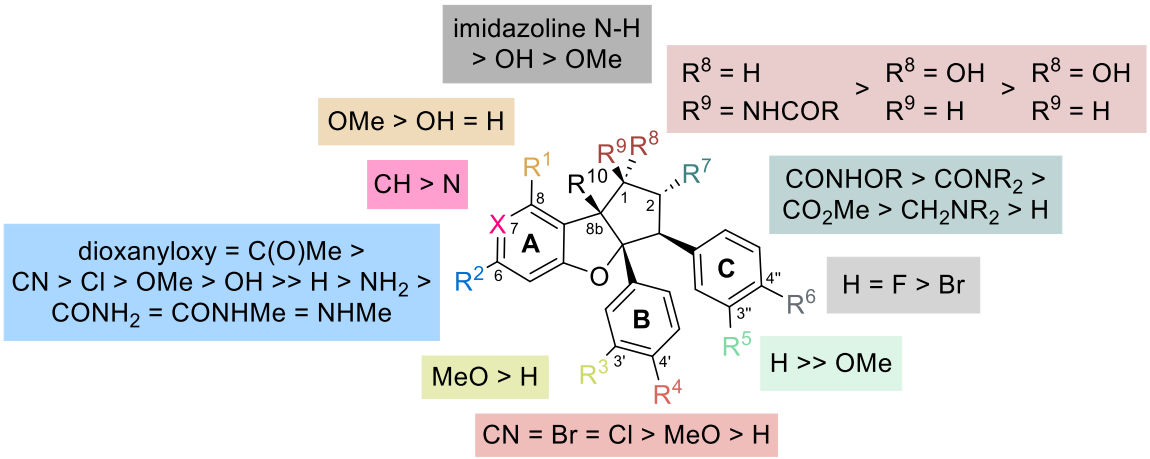


Figure 11 Summary of structure-activity relationships identified by previous studies on flavaglines.

A2 Project Aims

The aim of this project was the design and synthesis of novel rocaglamide (**9**) and silvestrol (**10**) derivatives for testing against various emerging viruses by collaborating partners at the Ruhr-University Bochum. Based on previous work in the literature, scalable, reliable and effective synthetic routes should be developed to prepare compounds with a wide range of modifications at various positions of the molecules scaffold.

The focus of the modifications should be on the substitution of the natural compound's methoxy groups (R^1, R^2 and R^3 in Figure 12). As described in Section A1.5, it is well-known that the substituents at C6 and C4' have a major influence on the activity. The C8 position has been poorly addressed, therefore diversification at this position have a great potential to contribute to new insights into the structure-activity relationships. For this purpose, the methyl esters of the synthetic flavaglines should first be prepared and tested. Since it is known from the work of PORCO *et al.*[63,64] that the replacement of the ester by an *N*-methoxyamide can increase the activity by a factor of five to ten, selected derivatives with this motif should also be provided.

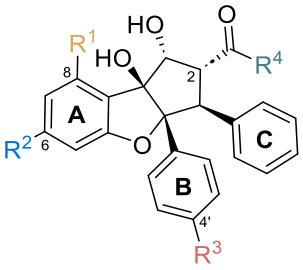


Figure 12 Scaffold of flavaglines with highlighting of positions to be modified within the scope of this dissertation.

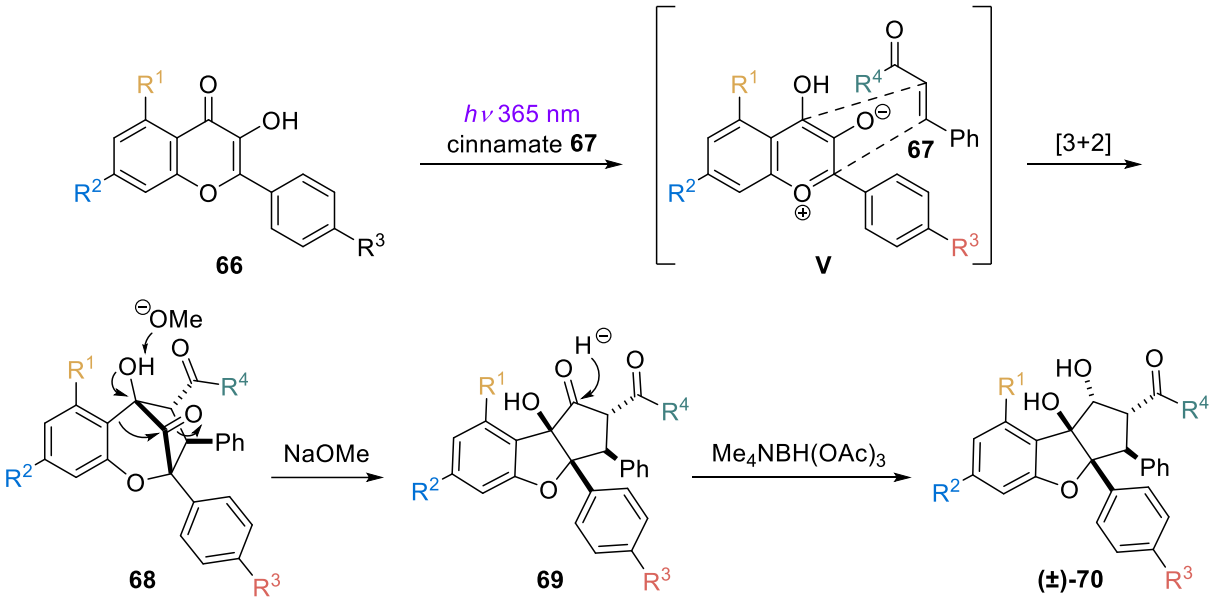
A further aim was to develop analogues mimicking the binding affinity of silvestrol (**10**) to the arginine pocket of eIF4A. This should enhance the activity and reduce the dependency on the structure of the 4'-UTR of the RNA. However, these derivatives should be structurally simplified and more readily accessible in comparison to silvestrol (**10**).

A3 Results and Discussion

A3.1 Retrosynthetic Analysis

In addition to flavaglines prepared in medicinal chemistry studies, there are a large number of total syntheses of natural flavaglines in the literature.[70,71,72] These syntheses are based on fundamentally diverse strategies and offer different opportunities to incorporate modifications during the routes that lead to novel rocaglamide and silvestrol derivatives. The selection of strategies for this work was focused on scalable, reliable and effective synthetic routes. A broad substrate scope was also essential in order to be capable of mapping a spectrum of derivatives as diverse as possible.

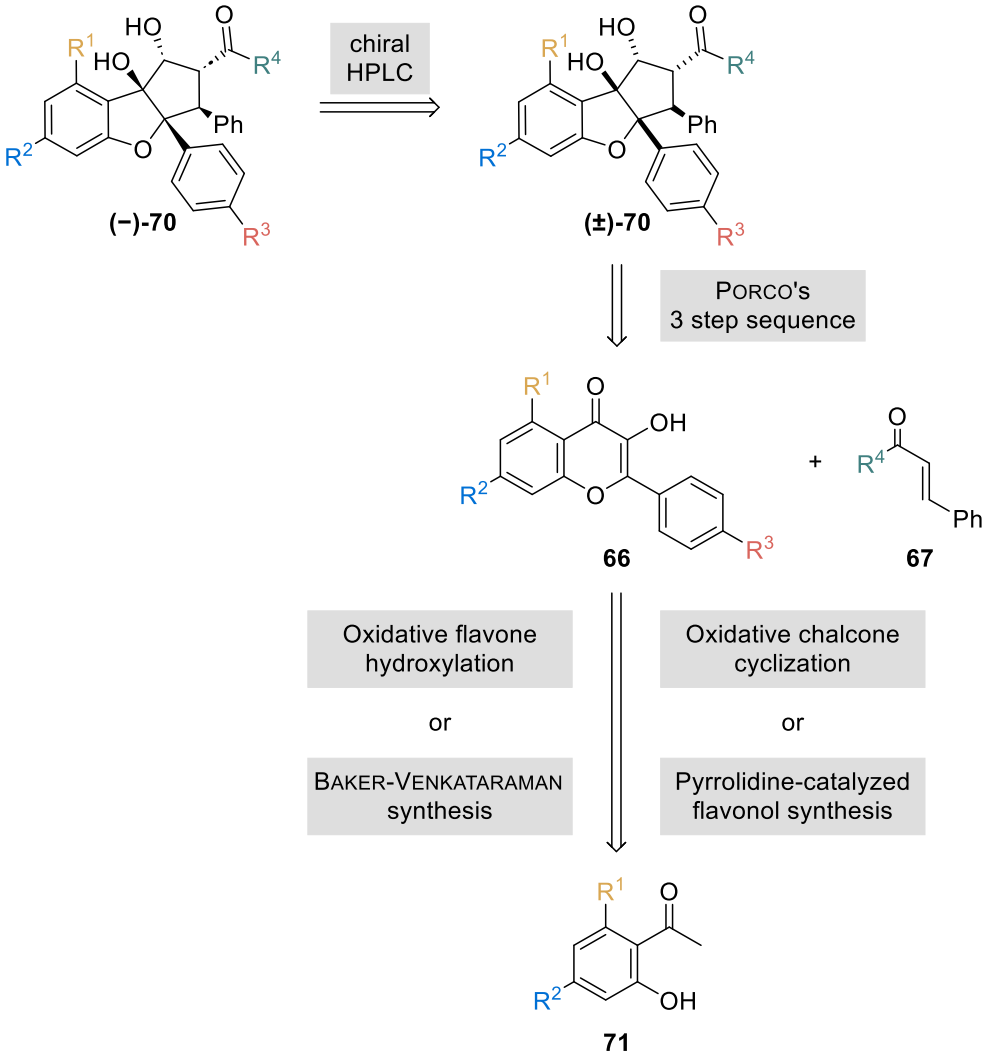
The most effective approach to date for the synthesis of flavaglines was developed by PORCO and co-workers in 2004.[73] This biomimetic approach, illustrated in Scheme 9, is based on a photochemical [3+2] cycloaddition starting from a flavonol **66** and a cinnamic acid derivative **67**. Irradiation of flavonol **66** by UV-A light leads to the formation of oxidopyrylium species **V** by excited-state intramolecular proton transfer (ESIPT). Dipolar cycloaddition gives rise to aglain derivative **68**, as in the postulated biosynthetic pathway (cf. Scheme 8). A subsequent base-mediated ketol shift yields the 1*H*-cyclopenta[*b*]benzofuran core **69**. The sequence is completed by an antiselective reduction of the ketone to form the flavagline **(±)-70**. All five adjacent stereocenters are diastereoselectivly established within only three steps.



Scheme 9 PORCO's biomimetic strategy for the synthesis of flavaglines.[73]

The disadvantage of this route is the lack of stereoinduction, resulting in a racemic mixture of the product. However, since it is well-known that only the (–)-enantiomers of rocaglamide and its derivatives are active and show significant cytotoxicity,[64] racemic mixtures were sufficient to compare the antiviral activity and biophysical properties of the synthetic flavaglines. Enantiomerically pure samples of selected candidates were obtainable by chiral HPLC (Scheme 10). Cinnamic acid derivatives **67** are commercially available or can be produced in a manageable number of steps. The synthesis of flavonols **66**, on the other hand, poses a considerably greater challenge. Diverse methodologies have been developed for accessing this class of natural products, all featuring their own distinct advantages and drawbacks in terms of practicality and substrate scope. In this work, four

of the most promising approaches were reviewed and tested on a number of structurally diverse substrates. Interestingly, all derive from *ortho*-hydroxy acetophenone **71**

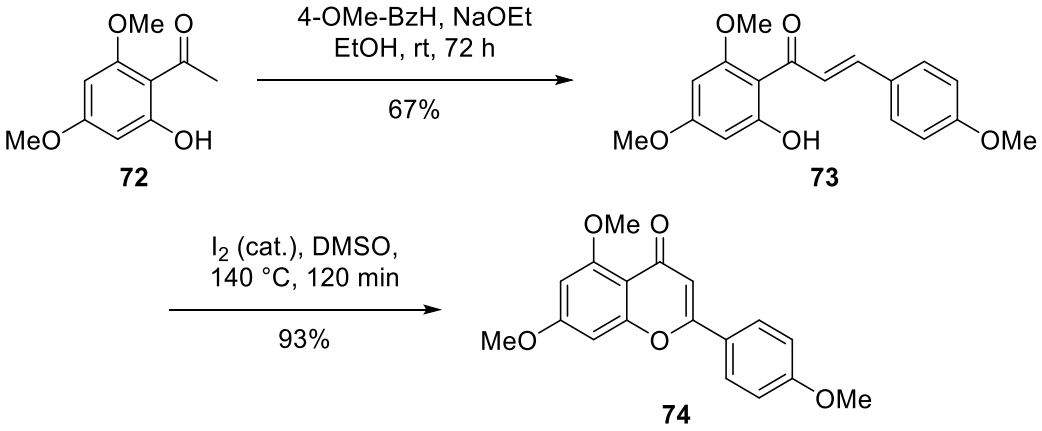


Scheme 10 Retrosynthetic analysis for the synthesis of antiviral flavaglines (**70**) which include rocaglamide (**9**) and silvestrol (**10**).

A3.2 Development of Synthetic Routes Towards Rocaglamide Derivatives

In order to find a suitable synthetic approach to the structural-versatile flavaglines, the literature-known methyl rocaglate (**59**) should first be prepared, which can easily be transformed into rocaglamide (**9**) and CR-31-B (**13**). All three compounds have served as important reference substances in the later biological tests.

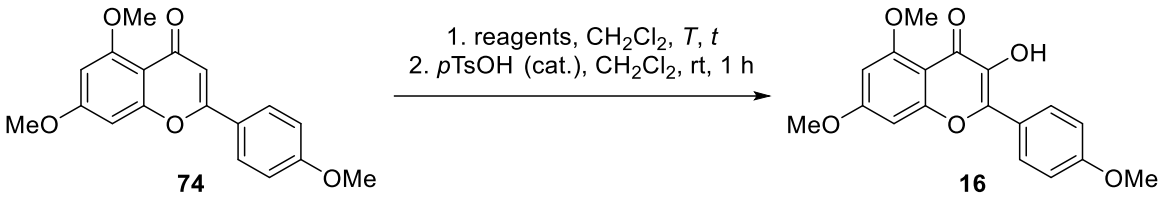
To synthesize flavagline **59** in accordance to the retrosynthetic analysis in Scheme 10, access to kaempferol 5,7,4'-trimethyl ether (**16**) had to be found. The first attempt was based on the epoxidation of the corresponding flavone **74** followed by acid-mediated ring opening using *p*TsOH as described by two independent groups.[74] For this purpose, compound **77** was synthesized from commercially available acetophenone **72** in two steps (Scheme 11). First, CLAISEN-SCHMIDT condensation with anisaldehyde based on a procedure by SALE and co-workers[75] afforded chalcone **73**, which was then oxidatively cyclized using a catalytic amount of iodine in DMSO.[76] Both steps were performed in good yields without the need for column chromatographic purification.



Scheme 11 Synthesis of flavone **74** from 2′-hydroxy-4′,6′-dimethoxyacetophenone (**75**).

With flavone **74** in hand, various conditions for the epoxidation were tested (Table 5). In literature, dimethyldioxirane (DMDO), *in situ* formed from a mixture of Oxone®, acetone and carbonate buffers in dichloromethane is mostly used for this transformation. Following the procedure of WANG *et al.*[77] only minimal transformation of the starting material was observed after 16 hours (Entry 1). Re-addition of all reagents after 20 hours and further stirring for 2 hours resulted in a yield of 20% (Entry 2). To improve this, an attempt was made to use DMDO solution in acetone freshly prepared according to TABER's procedure,[78] but only 9% yield was obtained (Entry 3). Since the conversion rate was very low in all experiments, it was hypothesized that better results could be obtained with the stronger oxidizing reagent methyl(trifluoromethyl)dioxirane (TFDO). In analogy to DMDO, TFDO was prepared *in situ* from Oxone®, 1,1,1-trifluoroacetone, $NaHCO_3$ and Na-EDTA solution.[79] However, only decomposition of flavone **77** was observed (Entry 4). Finally, classical SCHEFFER-WEITZ conditions applying lithium hydroxide and aqueous hydrogen peroxide solution were also attempted, but resulted in a mixture of side-products that are known to form upon the alkaline degradation of flavones (Entry 5).[80]

Table 5 Studies on the oxidative hydroxylation of flavone **74**.

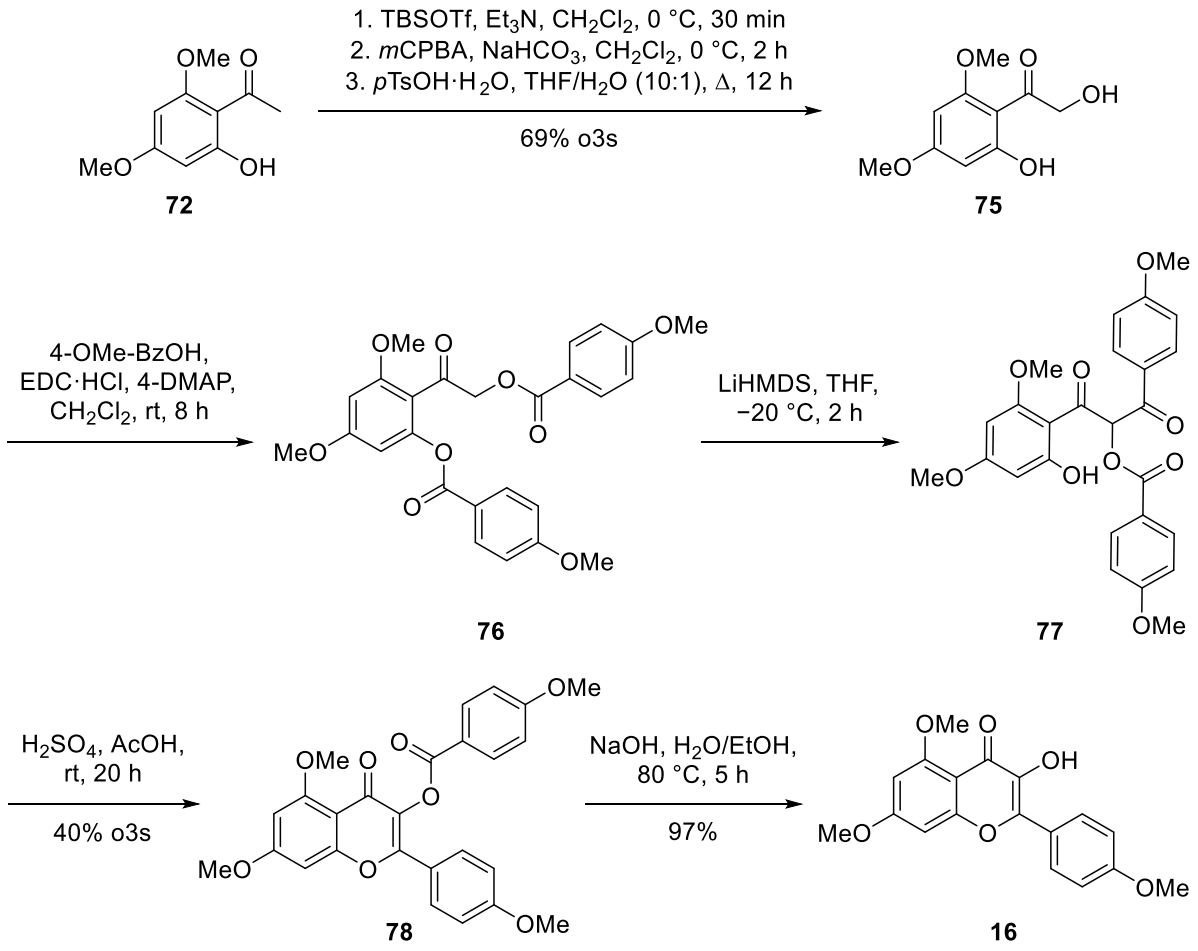


Entry	Reagents	*T* / °C	*t* / h	Yield
1	Oxone® (14.5 eq.), acetone, carbonate buffer	25	16	no conv.
2	Oxone® (14.5 eq.), acetone, carbonate buffer, after 22 h the same amount of all reagents was added again	25	24	20%[a]
3	DMDO solution (0.11 mM in acetone, 1.08 eq.)	25	24	9%[a]
4	Oxone® (5.00 eq.), 1,1,1-trifluoroacetone (11.0 eq.), $NaHCO_3$ (7.75 eq.), Na-EDTA solution	0	72	decomp.
5	H_2O_2 (3.00 eq.), LiOH (3.00 eq.)	0	62	decomp.

[a] Determined from product/product ratio in ^{1}H NMR of the crude product mixture

In addition to the poor conversion rates, purification of flavonol **16** from the reaction mixture posed difficulties. Recrystallization from various solvents was unsuccessful and column chromatographic separation from the starting material was found to be challenging. Especially on large scale, this route is therefore unsuitable for this project. Therefore, it is hardly surprising that this route, although promising rapid access to flavonols, has rarely been used in medicinal chemistry studies for the synthesis of flavaglines.

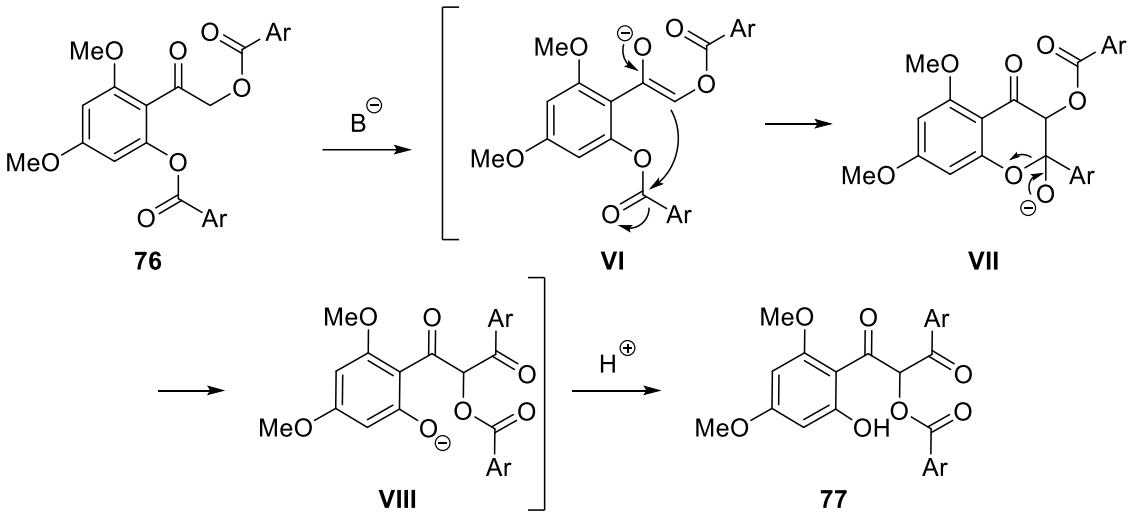
In contrast, the BAKER-VENKATARAMAN route has been utilized by PORCO's and TREMBLAY's groups, among others, although it requires considerably more steps and costlier reagents.[66,81,82] Consequently, this strategy was also tested for the synthesis of kaempferol 5,7,4'-trimethyl ether (**16**). The variant applied, shown in Scheme 12, was adopted from FUKASE *et al.*[82]. It proceeded from *ortho*-hydroxy acetophenone **72**, which was initially converted to α-hydroxy ketone **75** via a RUBOTTOM oxidation sequence. STEGLICH esterification of both alcohols with *p*-anisic acid provided the precursor **76** for the BAKER-VENKATARAMAN rearrangement. In the presence of the base LiHMDS, the anionic rearrangement led to 1,3-carbonyl compound **77** in excellent yield. The synthesis was continued with a ring-closing condensation reaction to form flavonol ester **78**. Subsequent saponification with sodium hydroxide gave corresponding flavonol **16** in 30% yield over seven steps.



Scheme 12 BAKER-VENKATARAMAN route for the synthesis of flavonol **16**.

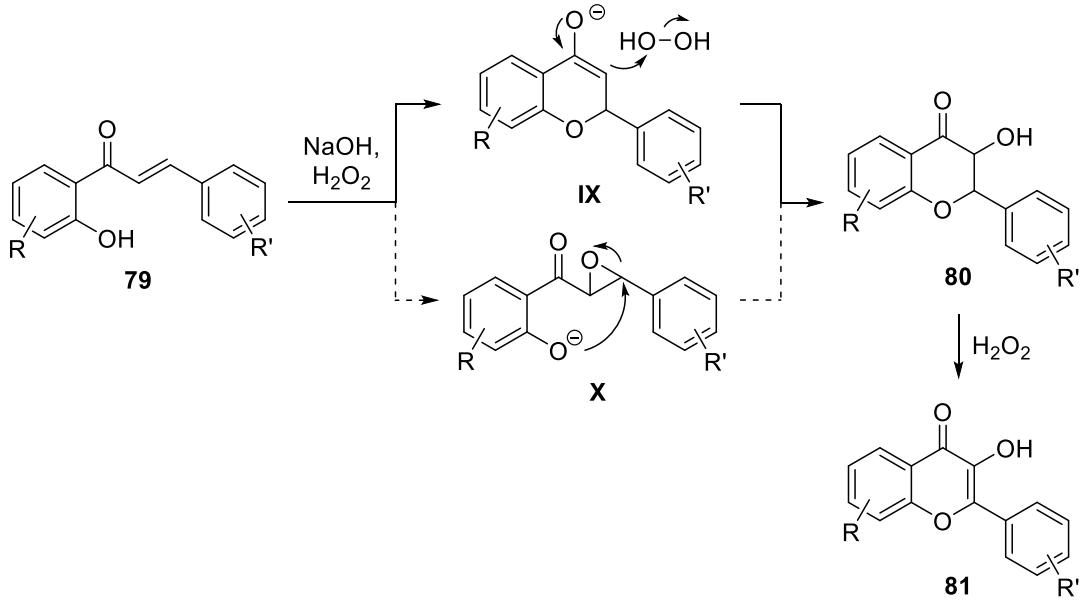
The mechanism of the key step, the BAKER-VENKATARAMAN rearrangement is shown in Scheme 13. Treating of diester **76** with LiHMDS leads to the formation of enolate **VI** which forms a six-membered ring by a nucleophilic attack to the carbonyl carbon of the phenolic ester. The tetrahedral intermediate

VII then collapses into a phenolate **VIII** which is subsequently protonated to give 1,3-carbonyl compound **77**.[83]



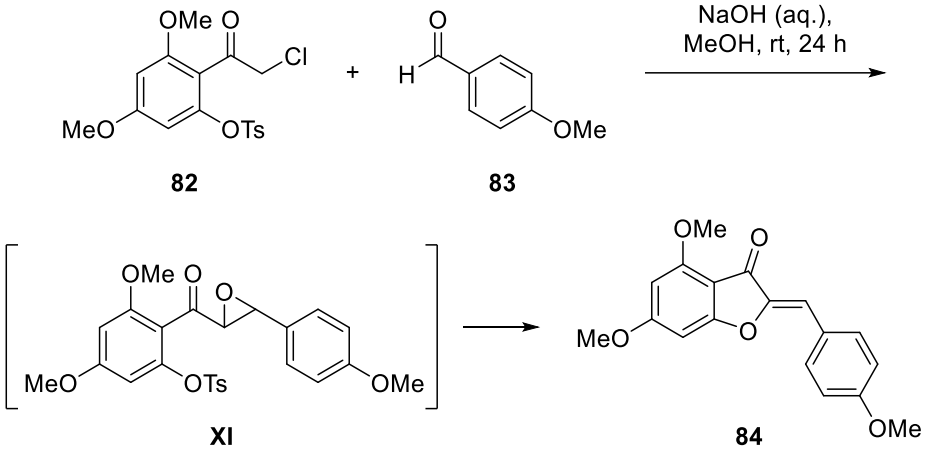
Scheme 13 Mechanism of the BAKER-VENKATARAMAN rearrangement.[83]

Since this pathway is comparatively long and requires harsh conditions incompatible with some intended modifications such as installation of nitriles or MOM-protected alcohols, a third strategy for the synthesis of flavonol **16** was tested. Similar to the biosynthesis of flavonols, the corresponding chalcone is the starting point. In an ALGAR-FLYNN-OYAMADA reaction, chalcone **79** is oxidatively cyclized under basic conditions. In the literature, two possible mechanisms have been proposed for this transformation (Scheme 14).[84,85] The first proceeds via MICHAEL addition of the phenolate to the *α*-*β*-unsaturated ketone and subsequent attack of the enolate **IX** on the hydrogen peroxide. The second starts with SCHEFFER-WEITZ epoxidation of the double bond and subsequent ring opening by the phenolate. In both cases, flavanonol **80** is formed and directly oxidized to the desired flavonol **81** by H_2O_2.



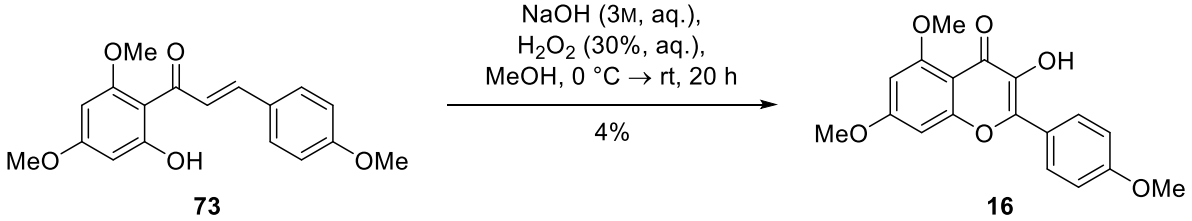
Scheme 14 Proposed mechanisms for the ALGAR-FLYNN-OYAMADA reaction.[85]

However, the first proposal seems to be more plausible, since O'SULLIVAN *et al.* have shown that epoxide **XI**, which can be formed *in situ* by a DARZENS reaction of compounds **82** and **83**, is converted exclusively to aurone **84** under basic conditions (Scheme 15).[86]



Scheme 15 DARZENS reaction of α-chloro ketone **82** and anisaldehyde (**83**) leads to formation of aurone **84**.[86]

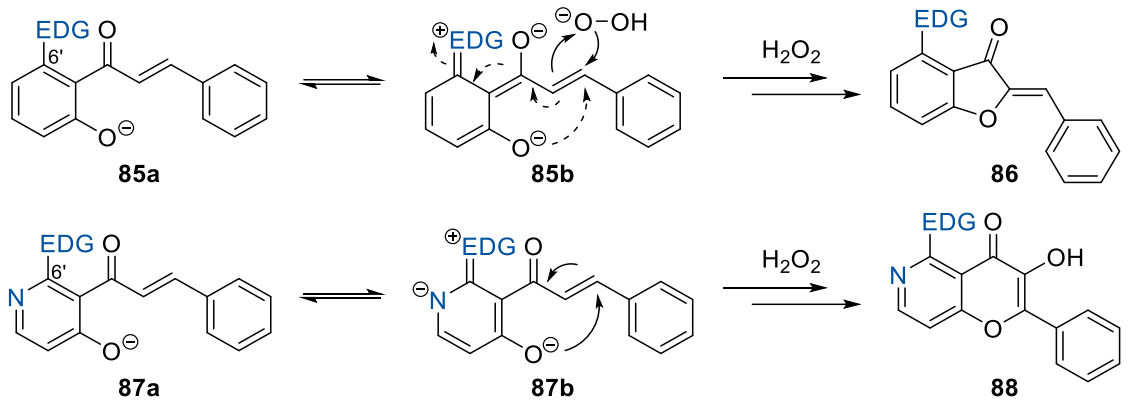
Chalcone **73** required for the formation of 5,7,4'-trimethyl ether (**16**) has already been prepared for the synthesis of flavone **74** (Scheme 11). For the ALGAR-FLYNN-OYAMADA reaction, conditions according to SALE *et al.* were applied (Scheme 16). The desired flavonol **16** was isolated in 4% yield. A major side product that was separable from the desired product by column chromatography was aurone **84**.



Scheme 16 ALGAR-FLYNN-OYAMADA reaction of 2′-hydroxy-4,4′,6′-trimethoxychalcone (**73**).

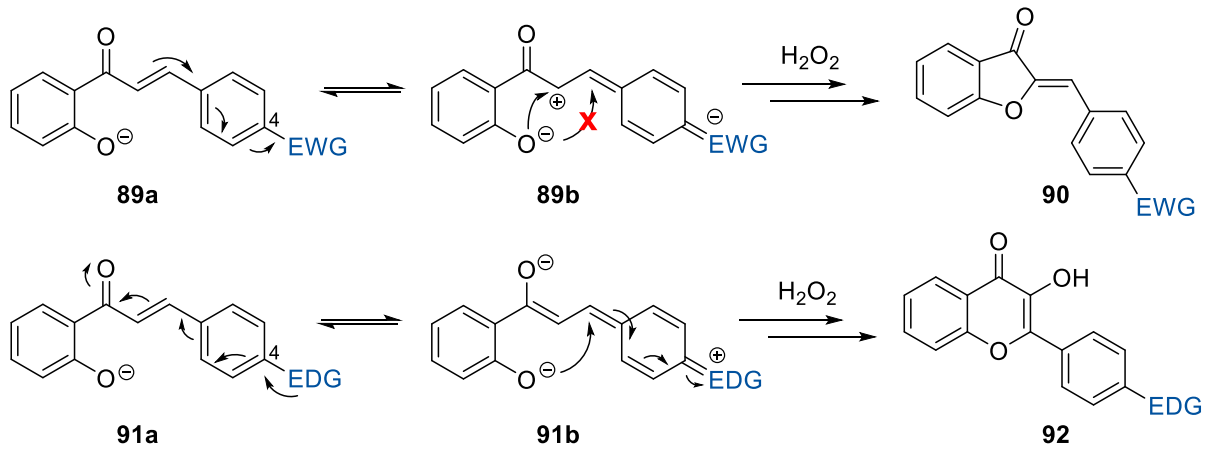
The ALGAR-FLYNN-OYAMADA reaction has been frequently applied within syntheses of flavaglines. In particular, this strategy was widely employed in the study of EFFECTOR THERAPEUTICS. However, it should be emphasized that only chalcones that were unsubstituted at C6' or contained a pyridine as A ring instead of a benzene were included in this work.[67] Further literature research revealed that substitution of the chalcone at C6' position in general leads to low yields in the ALGAR-FLYNN-OYAMADA reaction. In several cases, only the formation of the corresponding aurone was observed. It was suggested that steric interactions between the carbonyl group and the substituent at C6' are responsible for this selectivity.[86,87] However, since flavonols are preferentially formed from chalcones containing a pyridine A ring, even when substituted at C6', an additional electronic effect can be assumed. A feasible explanation is provided in Scheme 17. Chalcone **85a**, substituted with an electron donating group at the C6' position, is in equilibrium with its zwitterionic form **85b**. The latter is a 1,6-MICHAEL acceptor, which exhibit lower reactivity compared to 1,4-MICHAEL acceptors. This results in preferential epoxidation, leading to the formation of aurone **86**. In the case of pyridine **87a**,

however, the negative charge is stabilized by the nitrogen atom in the A ring. 1,4-MICHAEL addition is therefore preferred and the following steps afford flavonol **88**.



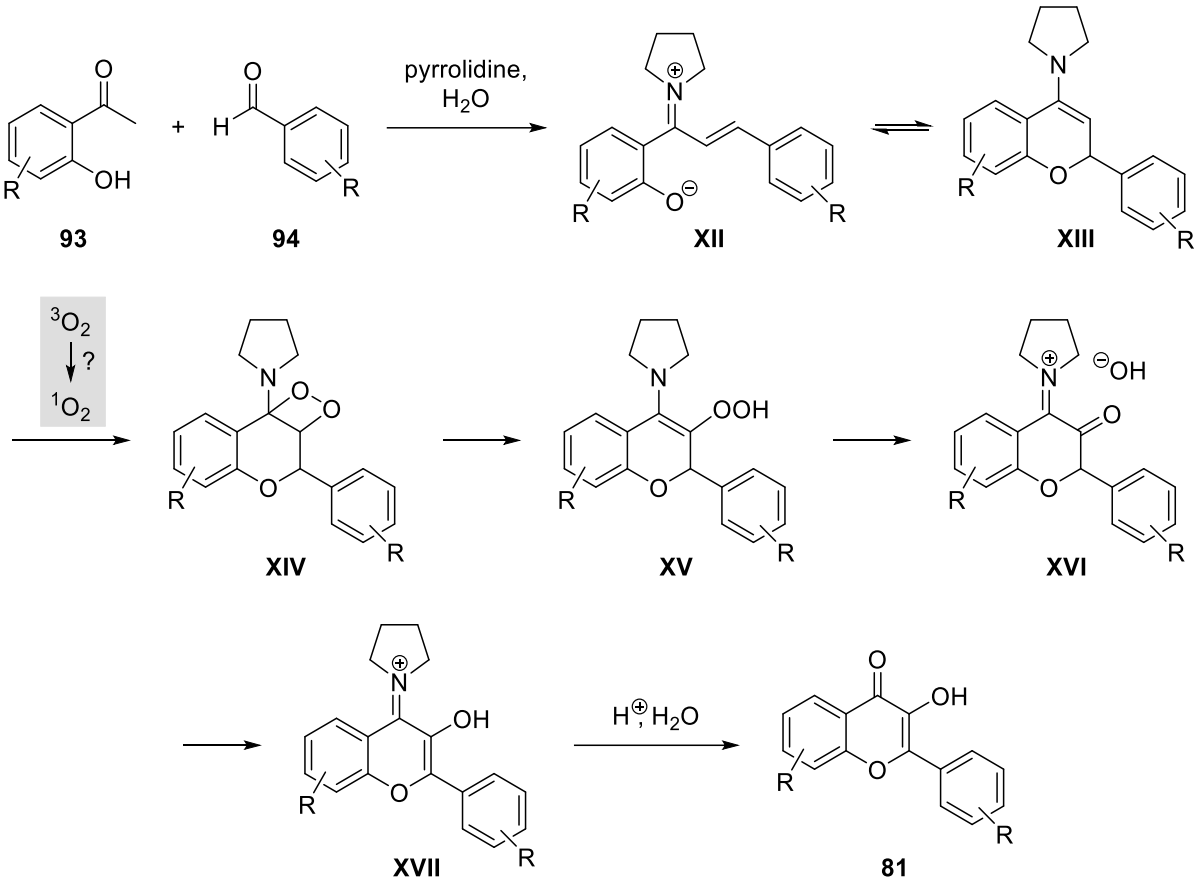
Scheme 17 Reasonable explanation for the selectivity of the ALGAR-FLYNN-OYAMADA reaction for 6'-substituted chalcones.

Furthermore, an electron-withdrawing substituent at C4 also results in poor yields. This could be due to a higher electron density and thus to a lower electrophilicity of the *β*-position of the ketone. An electron-donating substituent, on the other hand, has the opposite effect, leading to improved yields (Scheme 18).



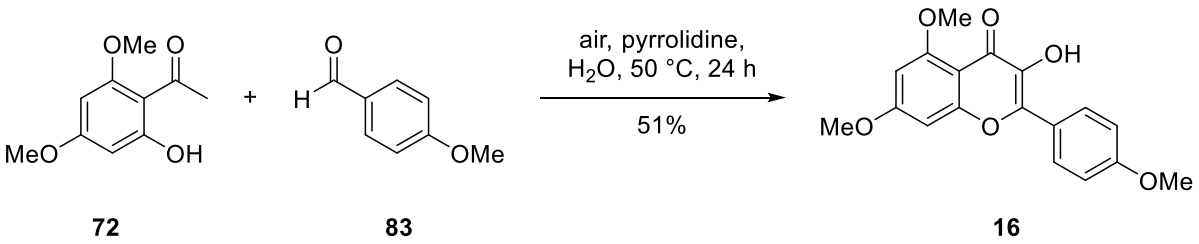
Scheme 18 Reasonable explanation for the selectivity of the ALGAR-FLYNN-OYAMADA reaction for 4-substituted chalcones.

The last method evaluated for the synthesis of flavonol **16** is closely related to the ALGAR-FLYNN-OYAMADA reaction. In 2020, WANG *et al.* reported on a pyrrolidine-catalyzed synthesis of flavonols.[88] Instead of hydrogen peroxide, atmospheric oxygen is employed as oxidant. The authors postulated that in a suspension of an *ortho*-hydroxy acetophenone **93** and benzaldehyde derivative **94** in pyrrolidine and water, the zwitterionic chalcone-type species **XII** is formed which can cyclize to enamine **XIII** (Scheme 19). This compound is subsequently oxidized by a [2+2] reaction with singlet oxygen to give dioxetane **XIV**. Ring opening and several rearrangement steps finally lead to iminium species **XVII**, which is converted into the desired flavonol **81** by aqueous acidic workup. The mechanism for the formation of the reactive oxygen species from atmospheric oxygen has not been fully elucidated. However, it is assumed that pyrrolidine and enamine **XIII** are primarily responsible for this result.[88]



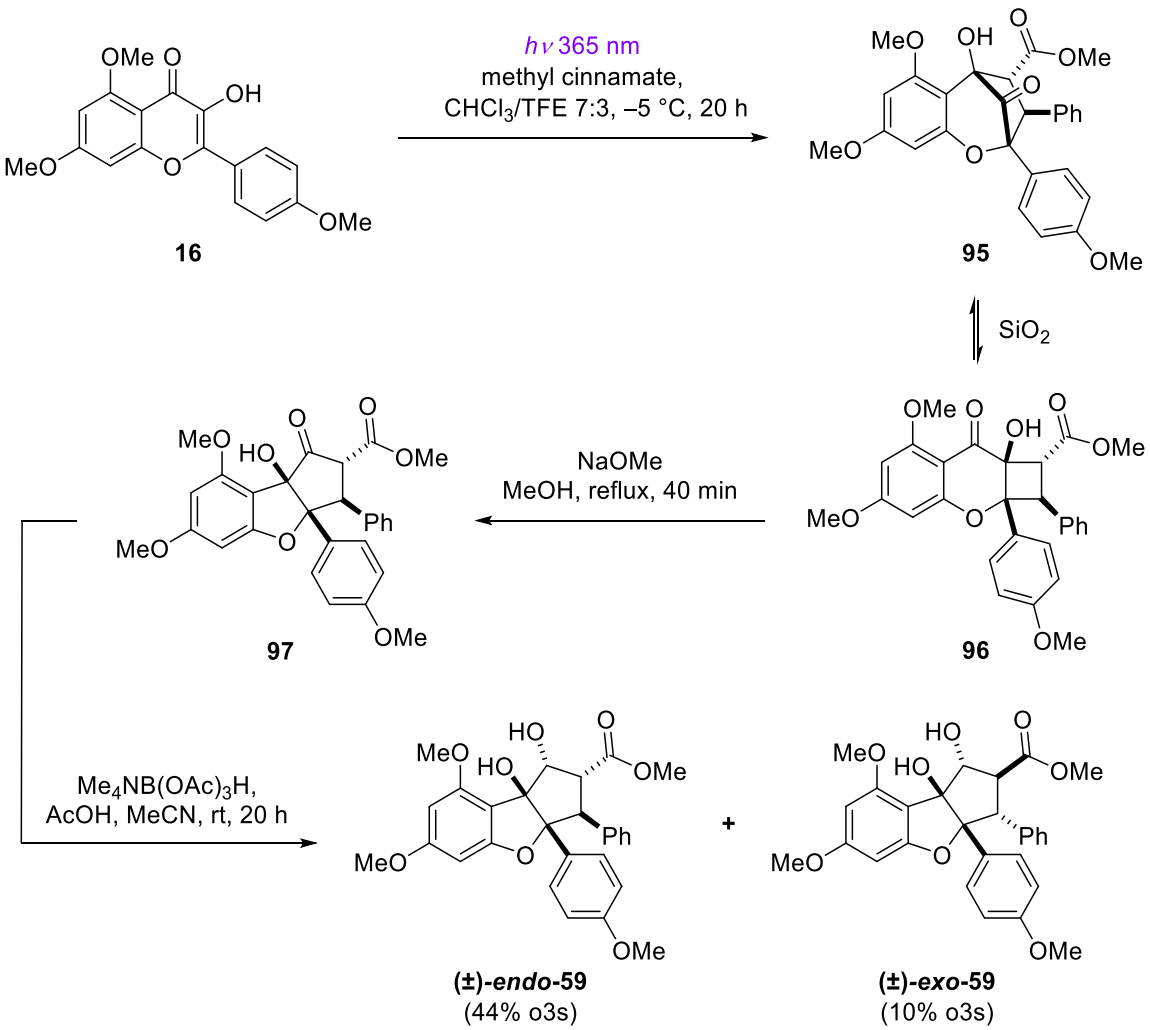
Scheme 19 Proposed mechanism for the pyrrolidine-catalyzed synthesis of flavonols.[88]

The substrate scope of the study revealed that this method also favors the formation of the aurone over the flavonol when electron-withdrawing substituents at C4 and electron-donating substituents at the C6' are combined. But in cases where only one of these structural motifs was present, yields were generally higher than for the ALGAR-FLYNN-OYAMADA reaction. This was also confirmed in this work by the synthesis of kaempferol 5,7,4'-trimethyl ether (**16**) in 51% yield (Scheme 20). It should be noted, however, that the outcome of the reaction is highly dependent on how well the starting materials are suspended in the pyrrolidine-water mixture. In several experiments, especially on a large scale, the formation of a two-phase mixture occurred. In these cases, only chalcone **73** could be isolated. The authors recommend the use of ethanol as co-solvent for multigram reactions, which, however, has a negative effect on the yield. Aprotic solvents such as acetonitrile, on the other hand, promote an alternative radical mechanism that lead to the formation of the corresponding aurone **84**.[88]



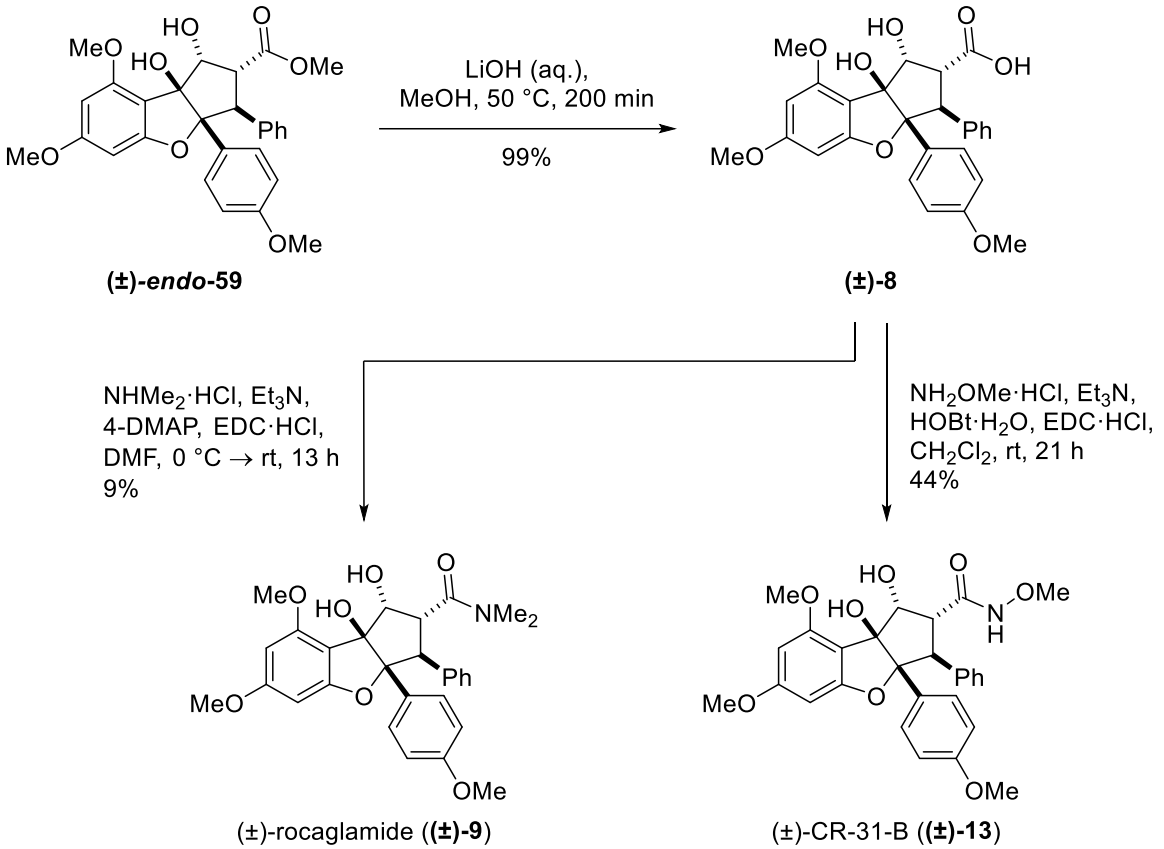
Scheme 20 Pyrrolidine-catalyzed synthesis of kaempferol 5,7,4'-trimethyl ether (**16**).

With successful strategies for the synthesis of flavonol **16** in hand, the final steps towards the formation of flavagline **59** were addressed. As described in Section A3.1, this was achieved following a biomimetic sequence described by PORCO *et al.*[73] The sequence shown in Scheme 21 started with a UV light-mediated [3+2] cycloaddition of flavonol **16** with methyl cinnamate. In the original publication, methanol was used as the solvent,[73] but subsequent studies revealed that a 7:3 mixture of chloroform and 2,2,2-trifluoroethanol (TFE) significantly enhanced the formation of the oxidopyrylium species **V** and thus improved the overall yield.[89] Another important factor was preventing self-condensation of flavonol **16** by adding a large excess of the cinnamic acid derivative. In this work, the procedure of RIZZACASA *et al.* was applied, which involved the use of 14.2 equivalents of methyl cinnamate.[90] The unconverted part was separated from the crude reaction mixture of *endo*- and *exo*-aglain **95** by column chromatography. As described in the literature,[73] rearrangement mediated by the slightly acidic silica was observed, resulting in benzo[*b*]cyclobutapyran-8-one **96**. However, this did not pose a problem since both compounds **95** and **96** underwent conversion to tetrahydro-1*H*-cyclopenta[*b*]benzofuran **97** with sodium methoxide. After subsequent *anti*-selective reduction under EVANS-SAKSENA conditions, the desired *endo*-methyl rocaglate (**(±)-*endo*-59**) was obtained in 44% yield over three steps. Additionally, the minor *exo*-product **(±)-*exo*-59** was isolated in 10% yield over three steps.



Scheme 21 Synthesis of **(±)**-methyl rocaglate (**(±)-*endo*-59**) from kaempferol 5,7,4'-trimethyl ether (**16**).

In order to synthesize the natural product rocaglamide (**(±)-9**) and its synthetic analogue CR-31-B (**(±)-13**) saponification of methyl ester **(±)-*endo*-59** was carried out. Using aqueous lithium hydroxide solution in methanol, the desired rocagloic acid (**(±)-8)** could be isolated in almost quantitative yield. Coupling with dimethylamine hydrochloride using 4-DMAP and EDC hydrochloride in dimethylformamide gave rocaglamide (**(±)-9**) in poor yield. In contrast, formation of CR-31-B (**(±)-13**) employing 4-DMAP and HOBt as coupling reagent in dichloromethane proceeded in a moderate yield of 44% (Scheme 22).

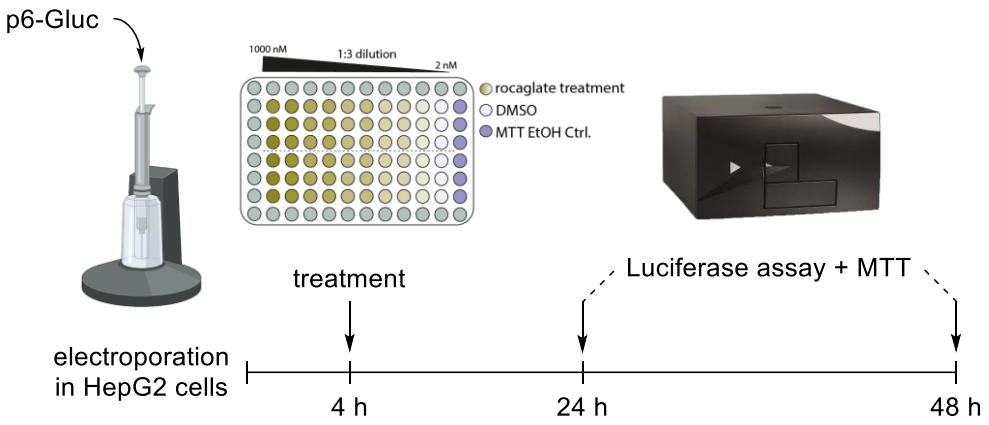


Scheme 22 Synthesis of (±)-rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**).

A3.3 In Vitro Antiviral Testing Against Hepatitis E

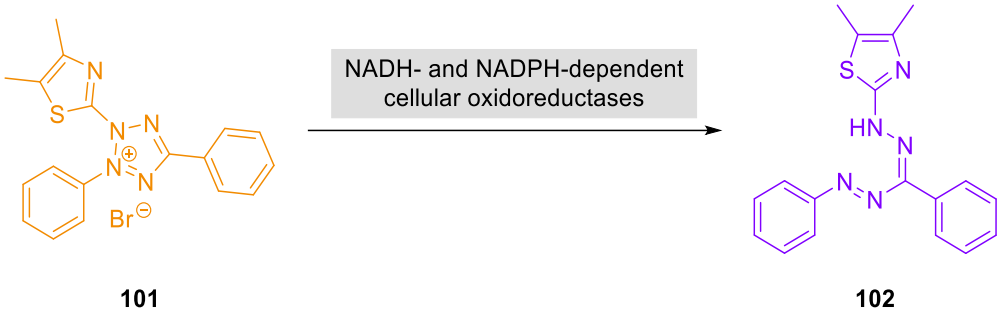
Flavaglines **(±)-*endo*-59**, **(±)-9** and **(±)-13** as well as all derivatives synthesized in the following sections were tested for their antiviral activity against hepatitis E (HEV) by members of the STEINMANN group at the Ruhr-University Bochum. HEV is a single-stranded positive sense RNA virus with a highly structured 5'-UTR that relies on cap-dependent translation for its replication. As explained in Section A1.3, eukaryotic initiation factor 4A (eIF4A) plays an important role in this process. Therefore, it can be assumed that clamping of eIF4A by flavaglines represents a potential target mechanism for antiviral therapy against HEV.[43]

To determine the inhibitory effect of the synthesized flavaglines on HEV replication, hepatoma cells (HepG2) were transfected with HEV-3 replicon p6-Gluc and then treated with solutions of the rocaglamide derivatives in DMSO at concentrations ranging from 0.15 nM to 1000 nM. Luciferase turnover was determined as a measure of HEV replication activity by luminescence measurements after 24 hours and 48 hours (Scheme 23).[91]



Scheme 23 Schematic representation of luminescence assay set-up.[91]

To investigate the cytotoxicity of the tested compounds, the metabolic activity of the treated cells, which strongly correlates with cell viability, was determined using an MTT assay after 24 hours and 48 hours. The colorimetric assay is based on the reduction of the pale-yellow dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, **101**) to its corresponding purple formazan **102** by NADH- and NADPH-dependent cellular oxidoreductase enzymes.[92,93]



101 **102**

Scheme 24 Underlying chemical reaction of the MTT assay.[93]

Based on the results of the luminescence measurements, dose-response curves were fitted to calculate IC_{50} and CC_{50} values. Additionally, a selectivity index (SI) was determined, which corresponds to the ration of the two values. In theory, the higher the SI ratio, the more effective and safer a drug would be in *in vivo* treatment of a viral infection. The ideal drug would be cytotoxic only at very high concentrations and would have an antiviral effect at very low concentrations, resulting in a high SI value.[94]

The results for the synthesized compounds (±)-methyl rocaglate (**(±)-*endo*-59**), (±)-rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**) as well as for an authentic sample of (−)-silvestrol (**10**) are presented in Table 6. For the comparison of the antiviral activity and the cytotoxicity, mainly the values after 48 h are considered, since the effects are usually more significant after a longer duration of exposure.

Table 6 IC_{50}, CC_{50} and SI values calculated for silvestrol (**10**), (±)-methyl rocaglate ((**±**)-***endo*-59**), (±)-rocaglamide ((**±**)-**9**) and (±)-CR-31-B ((**±**)-**13**) in HepG2.

Compound	24 h			48 h		
	IC_{50} /nM	CC_{50} /nM	SI	IC_{50} /nM	CC_{50} /nM	SI
(–)-silvestrol (**10**)[b]	4.10	139	33.8	2.76	16.1	5.84
(±)-methyl rocaglate ((**±**)-***endo*-59**)[a]	28.8	545	18.9	25.3	60.5	2.39
(±)-rocaglamide ((**±**)-**9**)[b]	29.4	494	16.8	18.3	55.1	3.01
(±)-CR-31-B ((**±**)-**13**)[b]	5.94	148	24.9	4.06	19.5	4.80

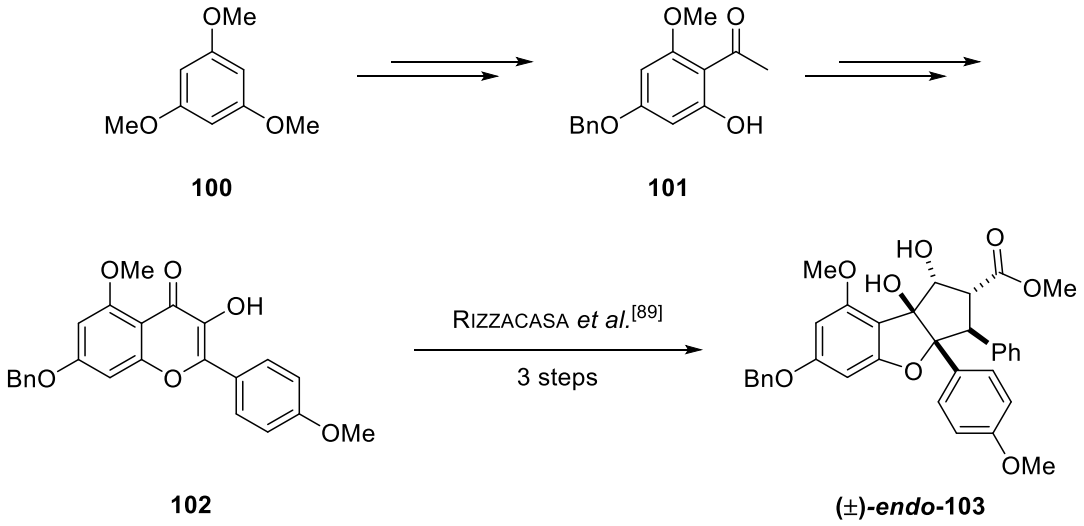
Mean values from multiple determinations ([a] $n = 2$; [b] $n = 3$)

The data obtained correspond well to the established structure-activity data from the studies of TREMBLAY and PORCO.[63,66] This clearly indicates that the anticancer and antiviral effects are indeed based on the same mechanism of action. Moreover, it becomes evident that the activity and cytotoxicity correlate, which is not surprising since flavaglines are also known to inhibit translation of a small number of cellular mRNAs (c.f. Section A1.3).

A3.4 Synthesis of C6-Protected Flavaglines and Late-Stage Diversification

In order to rapidly synthesize a large number of derivatives altered at C6 position by late-stage diversification, the preparation of protected flavaglines was sought. Inspired by previous work by TREMBLAY *et al.*,[66] the goal was to synthesize a 6-benzyloxy rocaglate **(±)-*endo*-103** which can be readily deprotected by hydrogenolysis.

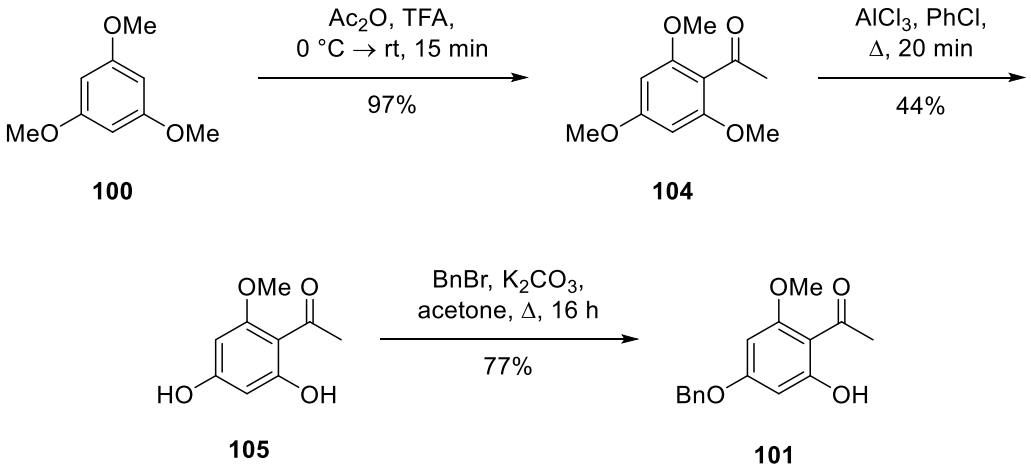
The literature-known synthetic approach started from the expensive flavone chrysin to first synthesize *ortho*-hydroxy acetophenone **101** by a rather inefficient process in terms of atomic economy. Therefore, a more efficient and scalable route was developed starting from 1,3,5-trimethoxybenzene (**100**) leading to compound **101**, in order to subsequently prepare flavonol **102** based on the strategies described in Section A3.2. For the final cycloaddition-rearrangement-reduction sequence, the conditions developed by RIZZACASA *et al.* were utilized, promising improved yields over those reported by TREMBLAY and co-workers (Scheme 25).[66,90]



Scheme 25 Intended synthetic pathway for 6-benzyloxy rocaglate **(±)-*endo*-103**.

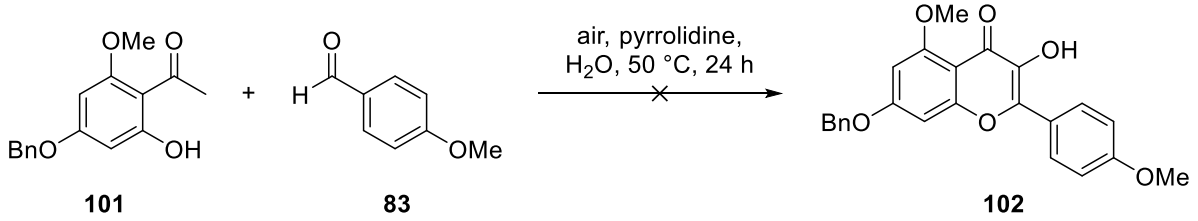
The first step of the synthesis illustrated in Scheme 26 was the acylation of 1,3,5-trimethoxybenzene (**100**). To ensure good scalability, a protocol from XU *et al.* for metal-free FRIEDEL-CRAFTS acylation was adopted.[95] Trifluoroacetic acid was applied as the solvent to form the mixed anhydride with acetic anhydride *in situ*. This activated species can be readily attacked by the electron-rich aromatic ring **100**. The desired acetophenone **104** was obtained in near quantitative yield in scales up to 25 g.
The selective deprotection of two methyl ethers mediated by the LEWIS acid aluminum trichloride presented a greater challenge. Due to the formation of a six-membered transition state, the deprotection of one of the *ortho*-methoxy groups is thermodynamically favored and therefore proceeded at first. The second demethylation occurred at the *para*-position due to steric effects. However, full selectivity could not be achieved. Moreover, cleavage of all three ethers was observed even before the starting material was fully converted. However, in multigram scale compound **105** could be isolated in 44% yield after purification by acid-base extraction.

Subsequently, selective protection of the *para*-hydroxy group could be carried out, since it was found to be more acidic than the one in the *ortho*-position, which is deactivated by a hydrogen bond to the carbonyl oxygen. Utilizing potassium carbonate as base, only the desired phenolate was formed, leading to *ortho*-hydroxy acetophenone **101** in 77% yield via an S_N1 reaction with benzyl bromide.



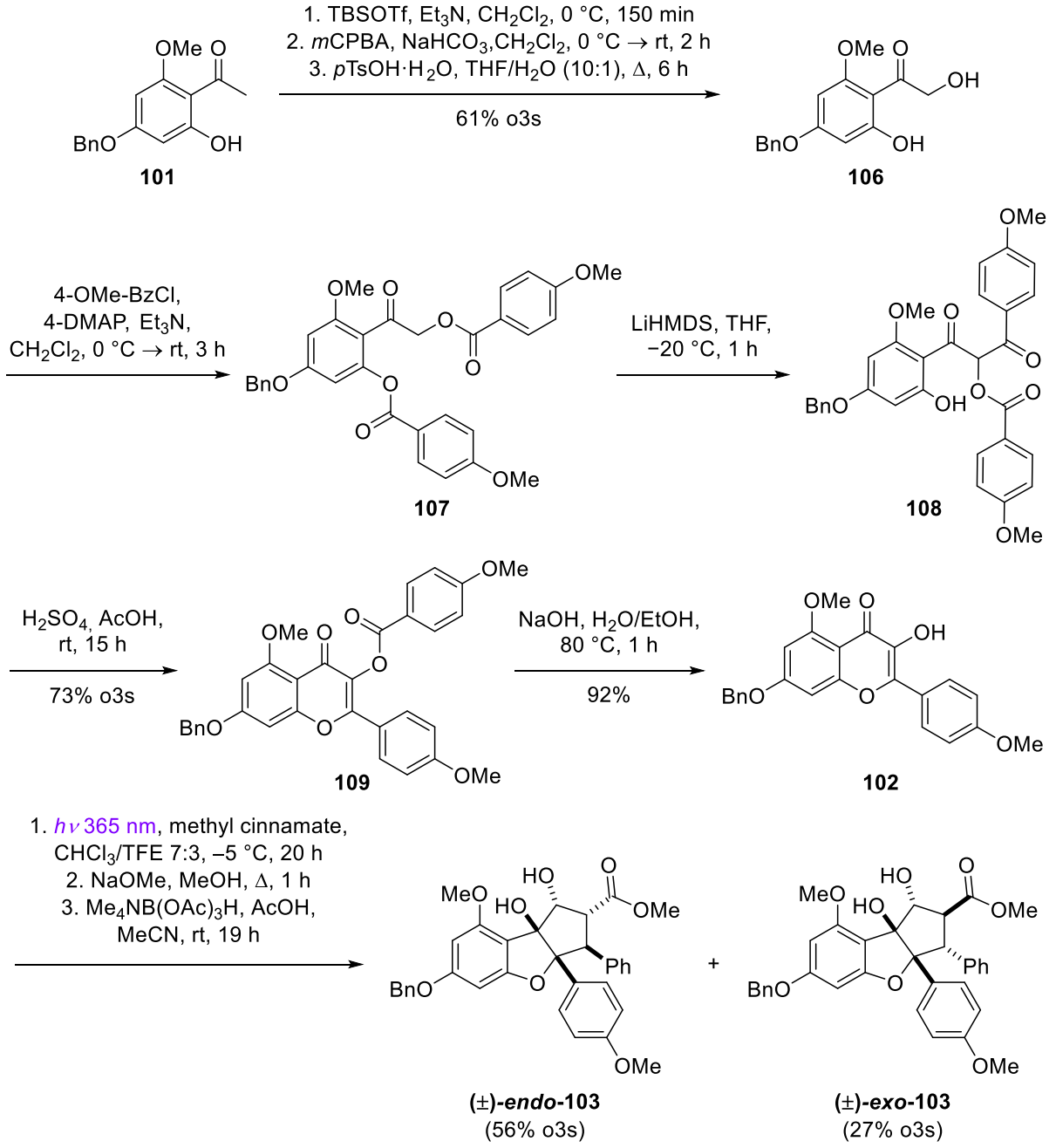
Scheme 26 Synthesis of *ortho*-hydroxy acetophenone **101**.

Flavonol **102** bears the same substituents at C5 and C4' as kaempferol 5,7,4'-trimethyl ether (**16**), which was successfully prepared via the pyrrolidine-mediated one-pot approach. Therefore, this method was also attempted for compound **102** (Scheme 27). However, no formation of the desired product was observed, probably due to the poor solubility of *ortho*-hydroxy acetophenone **101** in the pyrrolidine-water mixture.



Scheme 27 Attempted synthesis of flavonol **102** using the pyrrolidine-mediated one-pot method.

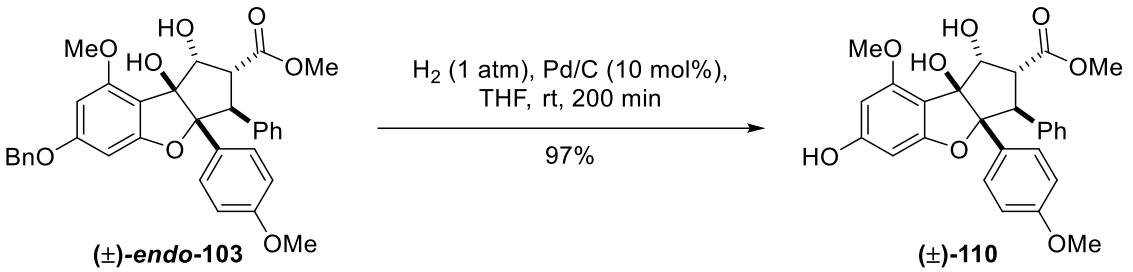
Thus, flavonol **102** was synthesized according to the BAKER-VENKATARAMAN route under the conditions reported by TREMBLAY *et al.*[66] (Scheme 28). The strategy succeeded in an equivalent manner to the preparation of kaempferol 5,7,4'-trimethyl ether (**16**). However, instead of a classical STEGLICH esterification of α-hydroxy ketone **106**, 4-methoxybenzoyl chloride was used in combination with triethylamine and a catalytic amount of 4-DMAP, which accelerated the esterification and led to an improved yield. The final sequence towards flavagline **(±)-*endo*-103** proceeded smoothly. The difficulties described by BEELER *et al.* in upscaling the UV light-mediated cycloaddition in batch could not be confirmed.[96] Even on a gram scale, high yields could be achieved for rocaglate **(±)-*endo*-103**.



Scheme 28 Preparation of flavonols **(±)-*endo*-103** and **(±)-*exo*-103** following the BAKER-VENKATARAMAN route.

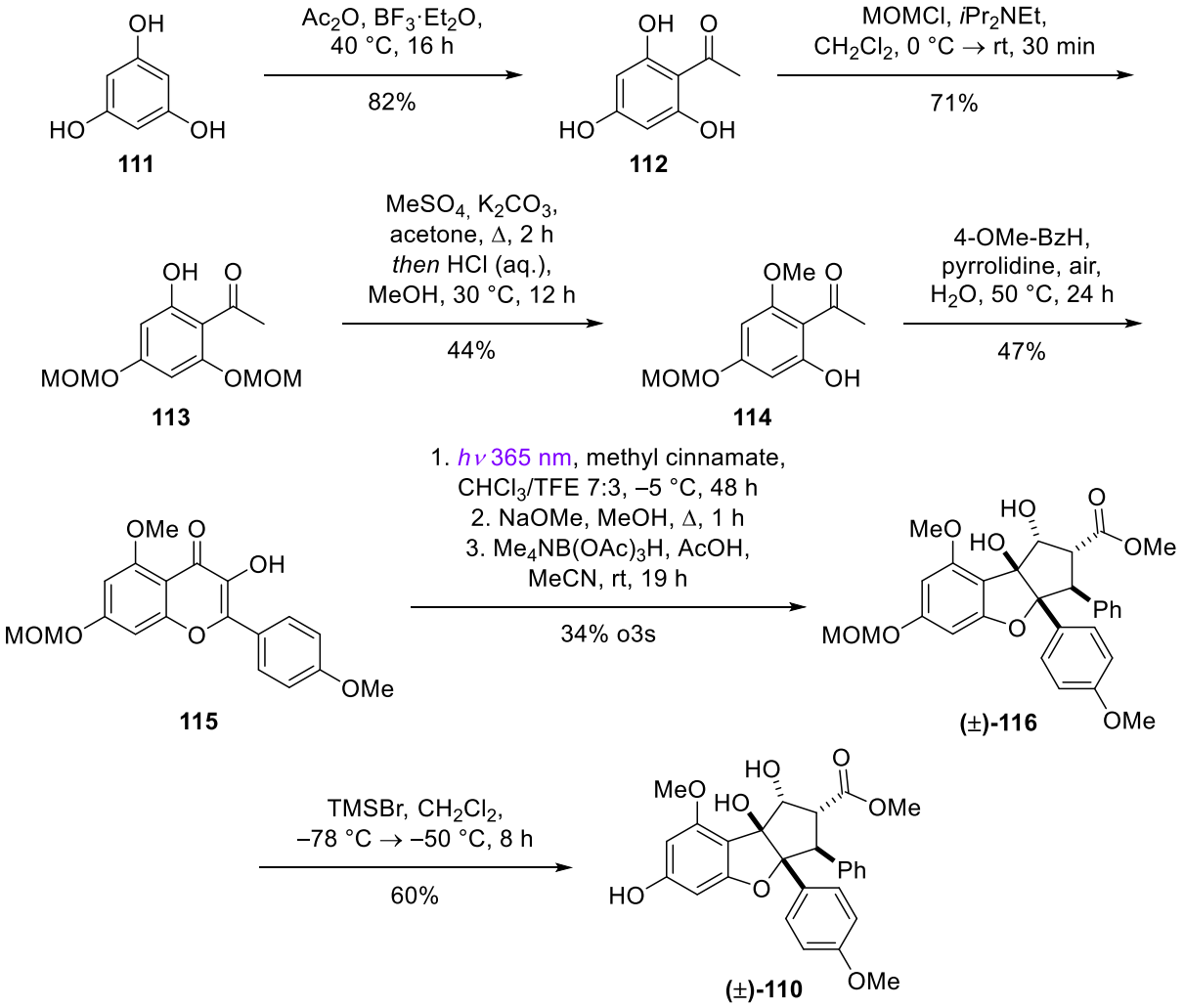
To test the capability of separating racemic mixtures of flavaglines, a sample of the 6-benzyloxy rocaglate **(±)-*endo*-103** was subjected to chiral preparative HPLC using the identical method described by RIZZACASA *et al.*[90] Chiral resolution was successful on small scales of up to 30 mg. The active

enantiomer **(–)-*endo*-103** could be obtained in 44% yield. However, for larger samples, enantiomerically pure samples could not be obtained. Therefore, late-stage diversification was performed with the racemic mixture. For this purpose, benzyl ether **(±)-*endo*-103** was deprotected by hydrogenolysis using palladium on charcoal under hydrogen atmosphere in almost quantitative yield (Scheme 29).



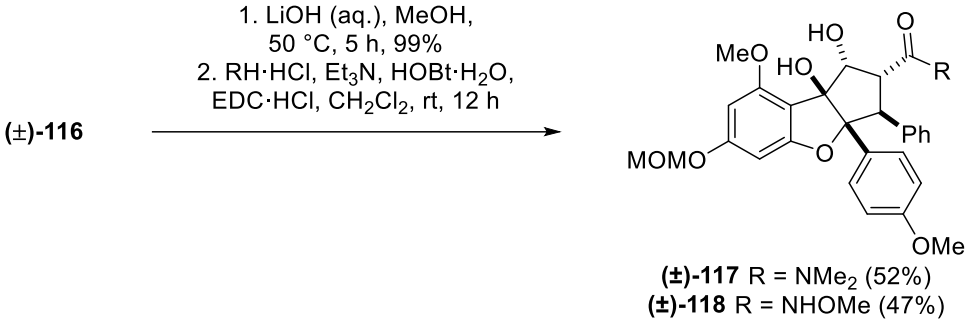
Scheme 29 Deprotection of 6-benzyl ether **(±)-*endo*-103** following a procedure by TREMBLAY *et al.*[90]

In total, 14 steps were required to obtain this intermediate compound with an overall yield of 7%. Since it was intended to prepare fairly large quantities of phenol **(±)-110** for diversification, development of a more efficient process was initiated (Scheme 31).



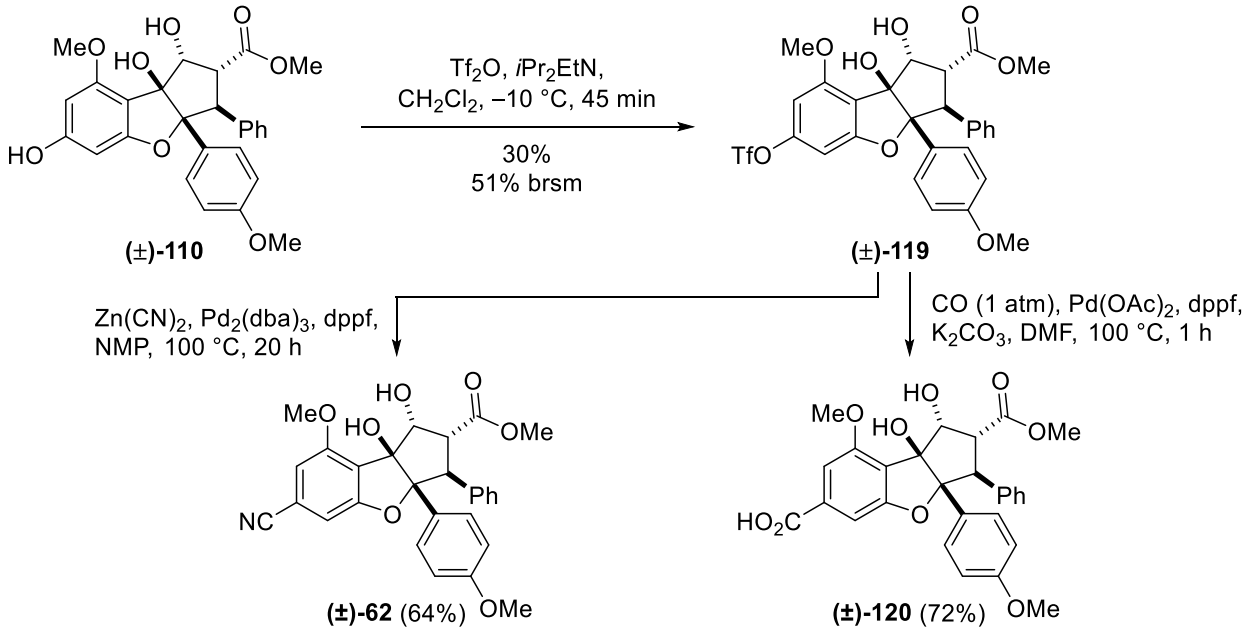
Scheme 30 Alternative synthetic route for the preparation of phenol **(±)-110**.

As known from the substrate scope reported by WANG *et al.*, *ortho*-hydroxy acetophenones featuring methoxymethyl ethers are well accepted for the pyrrolidine-catalyzed synthesis of flavonols.[88] Therefore, acetophenone **114** was synthesized from phloroglucinol (**111**) in a three-step sequence following literature-know procedures.[97] The subsequent one-pot reaction successfully delivered flavonol **115** in 47% yield. The cycloaddition-ketol-shift-reduction sequence then allowed the synthesis of 6-MOM-protected flavagline **(±)-116**. Finally, deprotection of the MOM ether with trimethylsilyl bromide was performed to give phenol **(±)-110** in 60% yield. Since the MOM group is known not only as a protecting group but also as a potential activity enhancing structural moiety of drug candidates,[98] 6-MOM analogues **(±)-117** and **(±)-118** of rocaglamide and CR-31-B were synthesized by saponification and amide coupling from methyl ester **(±)-116** as well (Scheme 31).



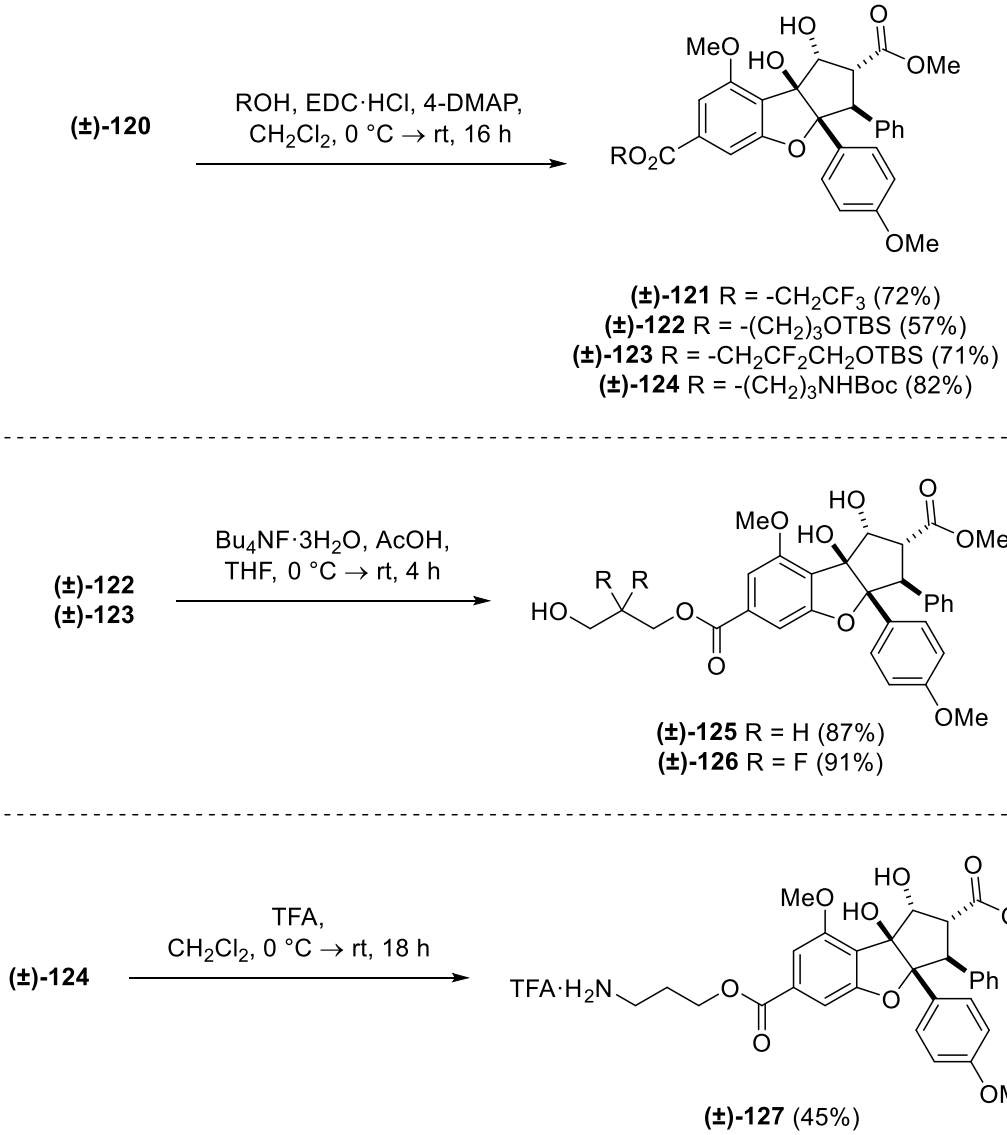
Scheme 31 Late-stage diversification of 6-MOM rocaglate **(±)-116.**

Phenol **(±)-110** offers the potential for etherification and esterification. In this work, a transformation to the corresponding triflate was intended, which has already been described by TREMBLAY *et al.* as substrate for palladium-catalyzed cross-coupling reactions.[66] The formation of triflate **(±)-119** was accomplished with trifluoromethanesulfonic anhydride in 30% yield (Scheme 32). The comparatively low yield is explained by the fact that full conversion could not be achieved. Subsequently, palladium-catalyzed cyanation and palladium-catalyzed hydroxycarbonylation were carried out to obtain flavaglines **(±)-62** and **(±)-120**.



Scheme 32 Cyanation and hydroxycarbonylation of triflate **(±)-119** synthesized from phenol **(±)-110**.

Both compounds have already been described by TREMBLAY and co-workers in 2012.[66] While the nitrile **(±)-62** was identified as an extremely potent selective translation inhibitor, no activity could be demonstrated for the carboxylic acid **(±)-120**. The corresponding methyl ester, on the other hand, is one of the most active rocaglamide derivatives described to date. A plausible explanation for the increased activity could be the fact that nitriles and carbonyl groups are much stronger hydrogen bond acceptors than the natural methoxy group.[99] In addition, the accepting atoms of the synthetic analogues are farther from the A ring than in the natural product, what could result in a greater spatial proximity to the potential hydrogen bond donor, leading to increased stability of the flavagline-eIF4A-RNA complex. Based on these assumptions, a series of carboxylic acid esters were synthesized (Scheme 33).



Scheme 33 Syntheses of carboxylic acid esters **(±)-121** – **(±)-127**.

The focus was on the synthesis of esters designed to mimic the binding affinity of silvestrol (**10**) to the arginine pocket of eIF4A. The aim was to combine the activity-enhancing effect of the carbonyl group with that of the dioxanyloxy group. The chain length of **(±)-125** and **(±)-127** was chosen to correspond to the distance between ring A and the secondary alcohol in the C5''' position of silvestrol (**10**) (Figure 13).

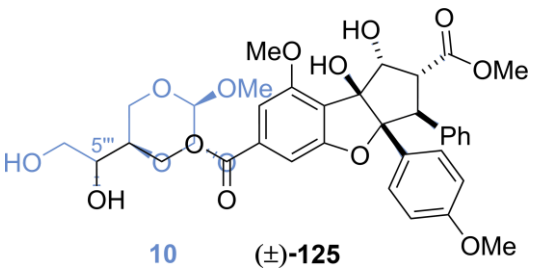


Figure 13 Superimposed structures of silvestrol (**10**) and the silvestrol-mimicking ester **(±)-125**.

In addition, ester **(±)-126**, a fluorinated analogue of compound **(±)-125**, was synthesized. Fluorine is an element frequently employed in drug design to substitute hydrogen atoms as its steric properties are comparable to those of hydrogen, but its electronegativity is significantly higher (3.98 on the PAULING electronegativity scale compared to 2.20 for H).[100] Fluorine atoms can act as hydrogen bond acceptors,[101] which in the case of compound **(±)-126** could lead to the formation of a H-bond to the terminal alcohol, thus slightly reducing the hydrogen bond donor character of the hydroxy group (Figure 14). Furthermore, with trifluoroethanol ester **(±)-121**, a compound was synthesized that does not possess a hydrogen bridge donor at the terminal position, making it incapable of interacting with arginine pocket of eIF4A.

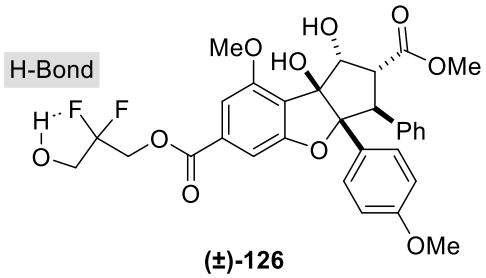
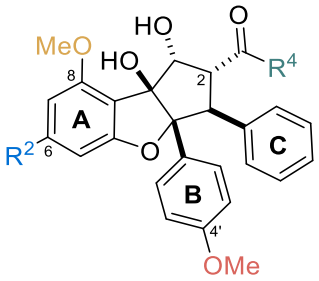


Figure 14 Formation of a hydrogen bond between terminal alcohol and fluorine atom of ester **(±)-126**.

Table 7 shows the results of the antiviral assays against HEV for the compounds obtained from the syntheses presented in this section in comparison to silvestrol (**10**), (±)-methyl rocaglate **((±)-*endo*-59**), (±)-rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**). The results revealed that only the *endo*-flavaglines exhibit antiviral and cytotoxic properties. A benzyl ether in C6 position significantly decreased the activity compared to the natural methyl ether. Similarly, 6-MOM ether **(±)-118** are only about half as effective as 6-methoxy analogues **(±)-9** and **(±)-13** after 24 hours, however, after 48 hours they are nearly about equally active. While conversion to triflate **(±)-119** resulted in a drop in activity, the nitrile **(±)-62** performed extremely well in the cell assay against HEV. Even as a racemic mixture, it was similarly potent as enantiomerically pure **(–)**-silvestrol **10**. Similarly, excellent results were seen for esters **(±)-125 – (±)-127**, in contrast to trifluoroethanol ester **(±)-121**, which is less potent. This corresponds well to the hypothesis suggesting the formation of a hydrogen bond to the arginine pocket which leads to improved stability of the enzyme-substrate-RNA complex. Although there is only a slight difference in activity between the three esters **(±)-125 – (±)-127**, an amine in the terminal position, which is a weaker hydrogen bond donor than a hydroxy group,[102] appears to be advantageous. In addition, weakening the hydrogen bond donor character by introducing fluorine atoms also resulted in minor improvements in activity.

Table 7 IC_{50}, CC_{50} and SI values calculated for the candidates discussed within this section in comparison to silvestrol (**10**), (±)-methyl rocaglate (**(±)-*endo*-59**), (±)-Rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**) in HepG2.



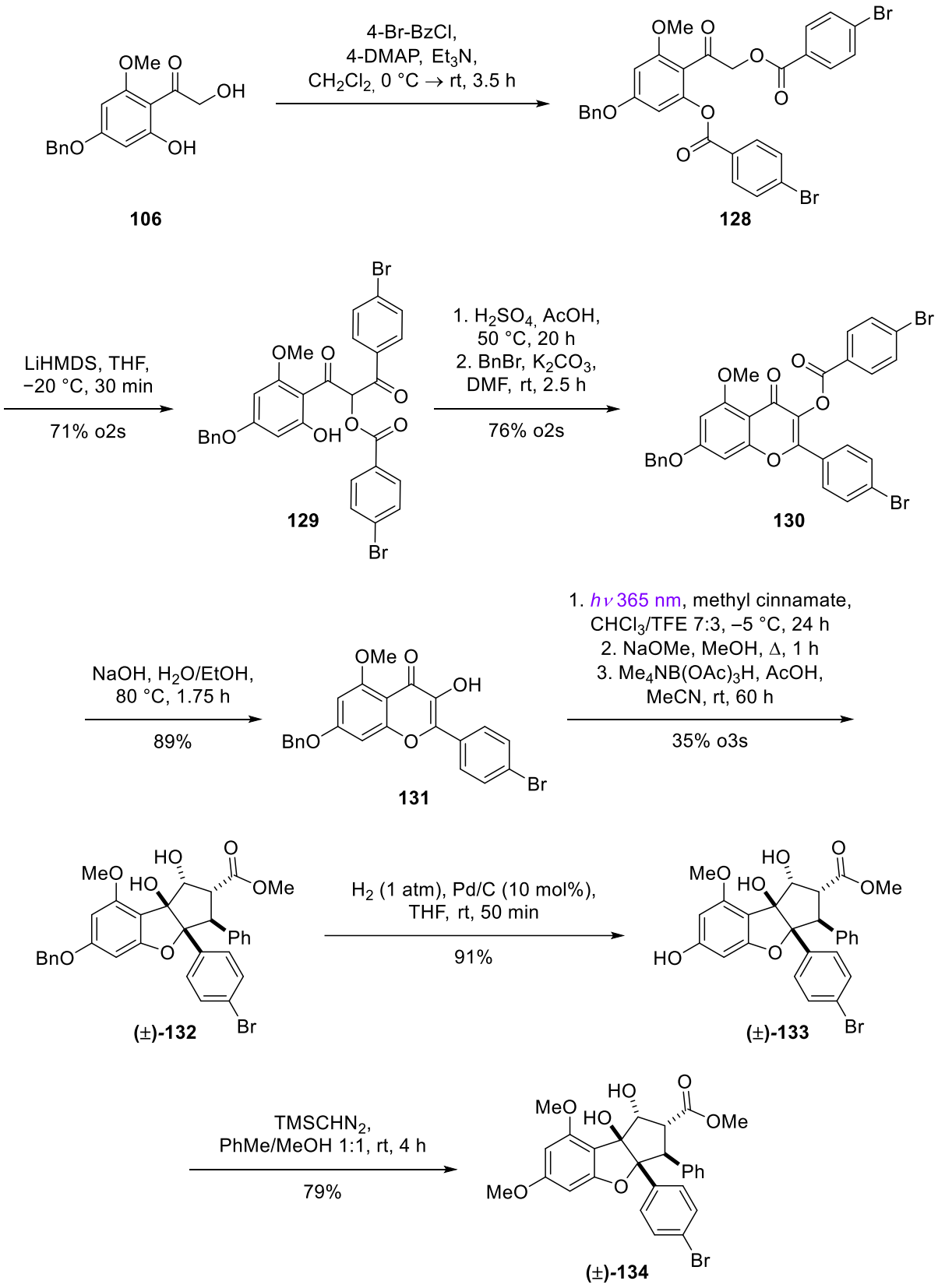
Compound	R^2	R^4	24 h IC_{50} /nM	24 h CC_{50} /nM	24 h SI	48 h IC_{50} /nM	48 h CC_{50} /nM	48 h SI
10[b]	dioxanyloxy	OMe	4.10	139	33.8	2.76	16.1	5.84
(±)-*endo*-59[a]	OMe	OMe	28.8	545	18.9	25.3	60.5	2.39
(±)-9[b]	OMe	NMe_2	29.4	494	16.8	18.3	55.1	3.01
(±)-13[b]	OMe	NH(OMe)	5.94	148	24.9	4.06	19.5	4.80
(±)-*endo*-103[a]	OBn	OMe	437	>1000	n.d.	413	453	1.10
(±)-*exo*-103[a]	OBn	OMe	>1000	>1000	n.d.	>1000	>1000	n.d.
(±)-118[a]	OMOM	NH(OMe)	10.4	268	25.7	5.86	22.3	3.80
(±)-119[a]	OTf	OMe	361	>1000	n.d.	377	468	1.24
(±)-62[a]	CN	OMe	3.58	162	45.3	3.39	10.7	3.16
(±)-121[a]	$-CO_2CH_2CF_3$	OMe	18.1	311	17.2	13.2	41.0	3.11
(±)-125[a]	$-CO_2(CH_2)_3OH$	OMe	7.71	132	17.1	6.18	15.4	2.50
(±)-126[a]	$-CO_2CH_2CF_2CH_2OH$	OMe	6.04	178	29.6	4.51	12.7	2.81
(±)-127[a]	$-CO_2(CH_2)_3NH_2{\cdot}TFA$	OMe	4.20	144	32.2	4.35	19.8	4.56

Mean values from multiple determinations ([a] $n = 2$; [b] $n = 3$)

A3.5 Synthesis of Halogenated Flavaglines

The introduction of halogens into active ingredients has become an influential factor in modern agrochemical and pharmaceutical research. Among drugs approved by the FDA until 2012, with the exception of biologics and peptides, the halogens fluorine, chlorine, bromine and iodine belong to the top 10 most abundant elements.[103] The introduction of halogens can affect the potency of a compound, change its physicochemical properties, or increase or decrease its metabolic and transformation susceptibility. The underlying reasons for these effects include steric properties, electronegativity and lipophilicity of the halogen atoms.[104]

For the flavaglines, it was reported that a chlorine atom at C6 or a bromine atom at C4' significantly increase the translation-inhibiting activity.[60,61,66] Substitution of the C8 methoxy group by a halogen atom has not yet been addressed. Likewise, synthesis of polyhalogenated derivatives of rocaglamide or silvestrol has not yet been reported. Therefore, a library of flavaglines was prepared by replacing the natural methoxy moiety with a halogen atom at the C6, C8 and/or C4' positions.



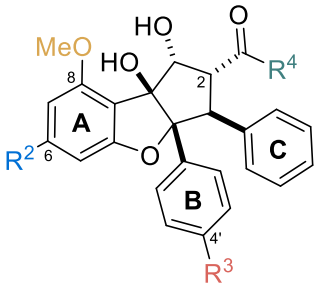
Scheme 34 Synthesis of 4'-bromo methyl rocaglate **(±)-134**.

Initially, the focus was on the C4' position, since the synthesis of the 4'-bromo rocaglate **(±)-*endo*-132** has already been described in literature.[66] The BAKER-VENKATARAMAN route was chosen in an equivalent manner to the preparation of derivative **(±)-*endo*-13**. The starting point was α-hydroxy

acetophenone **106**, synthesized as outlined in the preceding section. Instead of *para*-anisoyl chloride 4-bromobenzoyl chloride was applied for the esterification. The lithium hexamethyldisilazide-mediated BAKER-VENKATARAMAN rearrangement proceeded in equivalent manner as for the 4-methoxy analogues **(±)-*endo*-59** and **(±)-*endo*-103** described before. However, it was found that the acid-catalyzed ring formation of compound **129** to flavonol ester **130** was not observed under the conditions that were successful within the previous syntheses. It was necessary to increase the reaction temperature to 50 °C to achieve conversion of the starting material. However, this also led to partial deprotection of the benzyl group, requiring the product mixture to be benzylated again. All subsequent steps proceeded under the same conditions and with similar yields as for the previous derivatives. Although compound **(±)-133** offered potential for further derivatizations, only the 6-methoxy ether **(±)-134** was synthesized within this work (Scheme 34).

In addition to 4'-bromo rocaglate **(±)-134**, the 4'-chloro and 4'-fluoro analogues **(±)-135** and **(±)-136** were synthesized by VICTORIA in a similar manner.[91] The results of the antiviral cell assays of the compounds, presented in Table 8, clearly indicate that a fluorine atom leads to lower activity, while a chlorine and even more pronounced a bromine substituent at the C4' position significantly increase the antiviral properties but also the cytotoxicity.

Table 8 IC_{50}, CC_{50} and SI values calculated for 4'-halogenated rocaglates in comparison to silvestrol (**10**), (±)-methyl rocaglate (**(±)-*endo*-59**), (±)-Rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**) in HepG2.



Compound	R^2	R^3	R^4	24 h			48 h		
				IC_{50} /nM	CC_{50} /nM	SI	IC_{50} /nM	CC_{50} /nM	SI
10[b]	dioxanyloxy	OMe	OMe	4.10	139	33.8	2.76	16.1	5.84
(±)-*endo*-59[a]	OMe	OMe	OMe	28.8	545	18.9	25.3	60.5	2.39
(±)-9[b]	OMe	OMe	NMe_2	29.4	494	16.8	18.3	55.1	3.01
(±)-13[b]	OMe	OMe	NH(OMe)	5.94	148	24.9	4.06	19.5	4.80
(±)-134[b]	OMe	Br	OMe	7.18	289	40.3	9.87	31.9	3.23
(±)-135[b]	OMe	Cl	OMe	19.5	400	20.6	16.3	45.7	2.80
(±)-136[b]	OMe	F	OMe	338	>1000	n.d.	266	440	1.65

Mean values from multiple determinations ([a] $n = 2$; [b] $n = 3$)

Based on these data, it can be concluded that the steric demand of the substituent on C4' has a crucial influence on the activity. The bond length and VAN DER WAALS radii of C–O bonds are larger than those of a C–F bond, but significantly smaller compared to C–Cl or C–Br bonds (Table 9).[104]

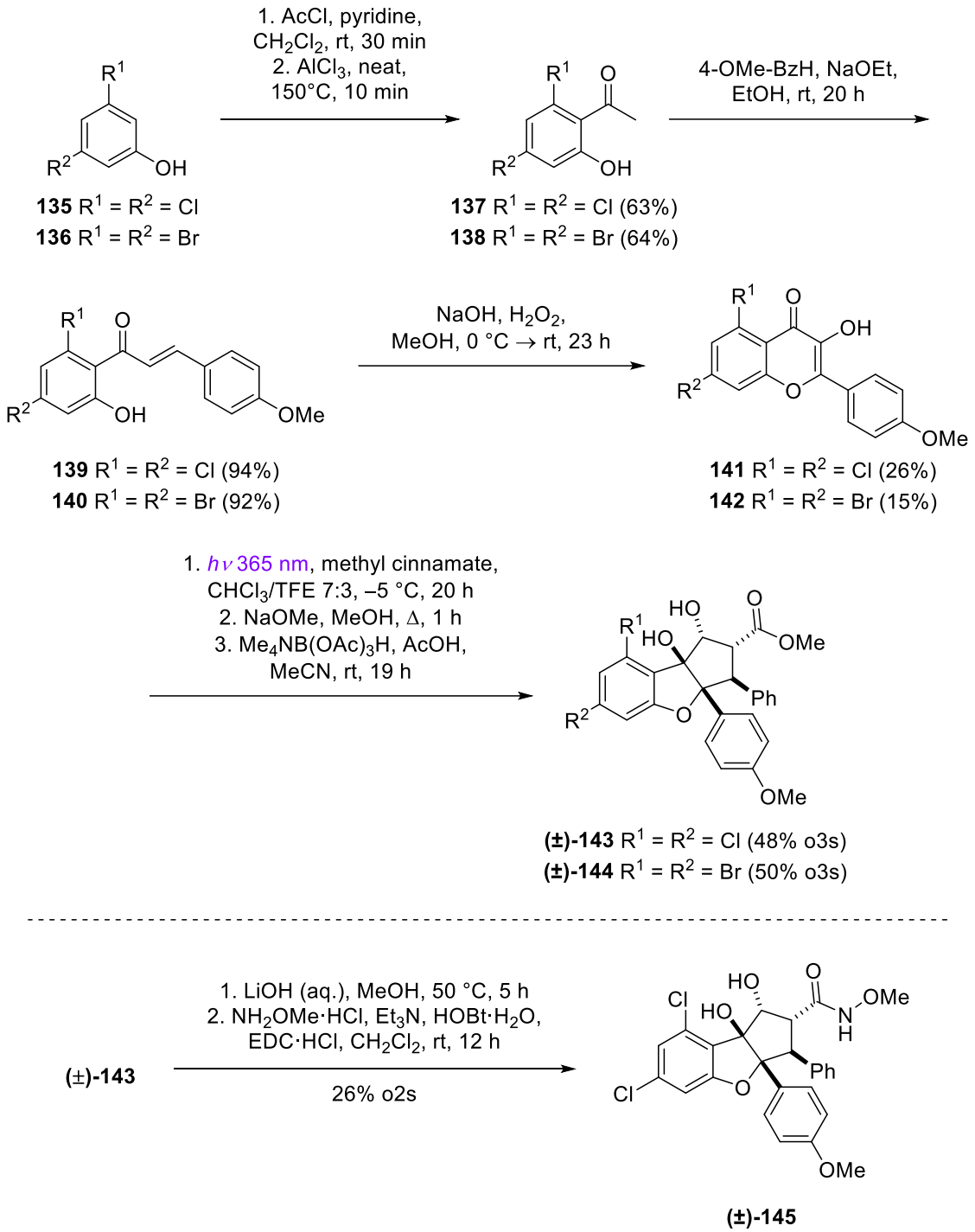
Table 9 Bond lengths, van der Waals radii and total size of carbon-halogen bonds.[104]

Bond	Length /Å	VAN DER WAALS radius /Å	Total size /Å
C–F	1.35	1.47	2.82
C–O–	1.43	1.52	2.95
C–Cl	1.77	1.80	2.57
C–Br	1.93	1.95	3.88

The next step was to incorporate the substitution of the methoxy groups at C6 and C8 positions. From a synthetic point of view, the 6,8-dihalogenated derivatives **(±)-143** and **(±)-144** represented attractive target structures. The precursor compounds 3,5-dihalophenols **135** and **136** are commercially available and the preparation of 5,7-dibromoflavonol **142**, which is a key intermediate in the synthesis of 6,8-dibromo flavagline **(±)-144**, has already been described in the literature by an ALGAR-FLYNN-OYAMADA reaction.[105]

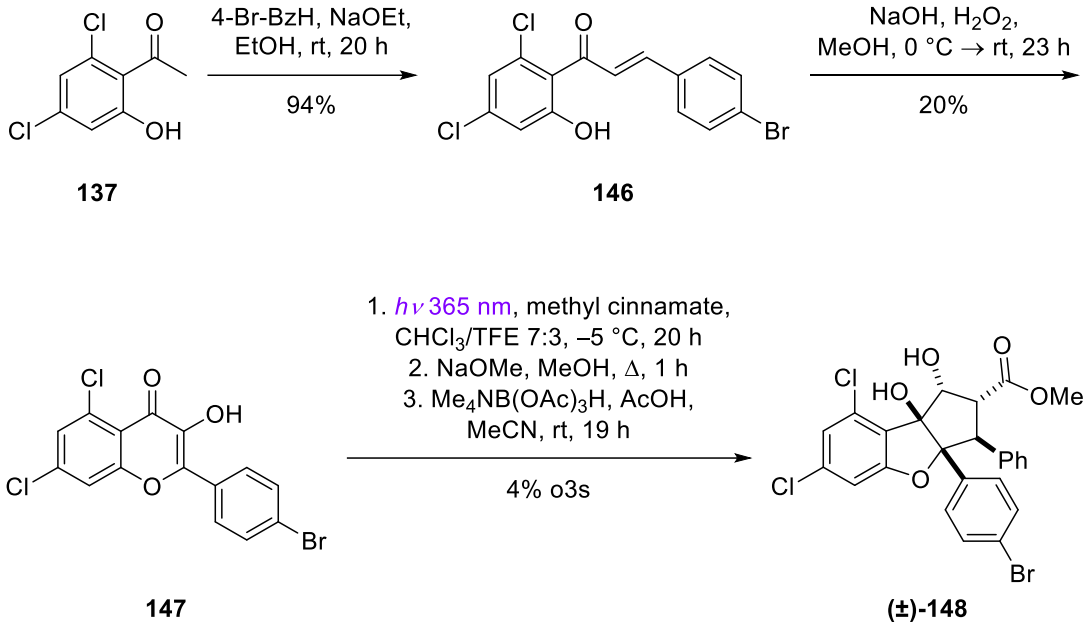
The syntheses of flavaglines **(±)-143** and **(±)-144**, illustrated in Scheme 35, commenced with the conversion of phenols **135** and **136** to the corresponding *ortho*-hydroxy acetophenones **137** and **138** following a protocol of SALE *et al.*[75] The procedure involved the initial acylation of the phenol using acetyl chloride and pyridine, followed by a FRIES rearrangement mediated by aluminum trichloride under solvent-free conditions at 150 °C. The exact mechanism of the FRIES rearrangement has not been elucidated to date. Evidence for intra- and intermolecular processes has been found.[106] Regioselectivity is explained by thermodynamic and kinetic reaction control. At elevated temperatures, the kinetically favored *ortho*-product is preferentially formed, whereas at room temperature, the thermodynamically favored *para*-acylation is observed in a higher proportion. Another important factor is the choice of solvent as in non-polar solvents or, as in the case of the syntheses of acetophenones **137** and **138**, under solvent-free conditions, the kinetic *ortho*-product is observed preferentially. Polar solvents cause the thermodynamic *para*-product to be formed to a greater extent, most likely by stabilizing an ionic transition state.[107]

With *ortho*-hydroxy acetophenones **137** and **138** in hand, chalcones **139** and **140** could be synthesized in excellent yields. ALGAR-FLYNN-OYAMADA reaction under the conditions reported ANEES and co-workers[105] afforded the 5,7-dihaloflavonols **141** and **142** in low to medium yields. Remarkably, all steps up to these key intermediates could be performed without the need for purification by column chromatography. This became necessary only in the final sequence to separate the methyl cinnamate after cycloaddition and the *exo*-diastereomer after the reduction step. The *endo*-methyl rocaglates **(±)-143** and **(±)-144** were both obtained in about 50% yield over three steps. In addition, 6,8-dichlorinated CR-31-B analogue **(±)-145** was synthesized by saponification and amide formation from compound **(±)-142** under the conditions presented in the previous sections.



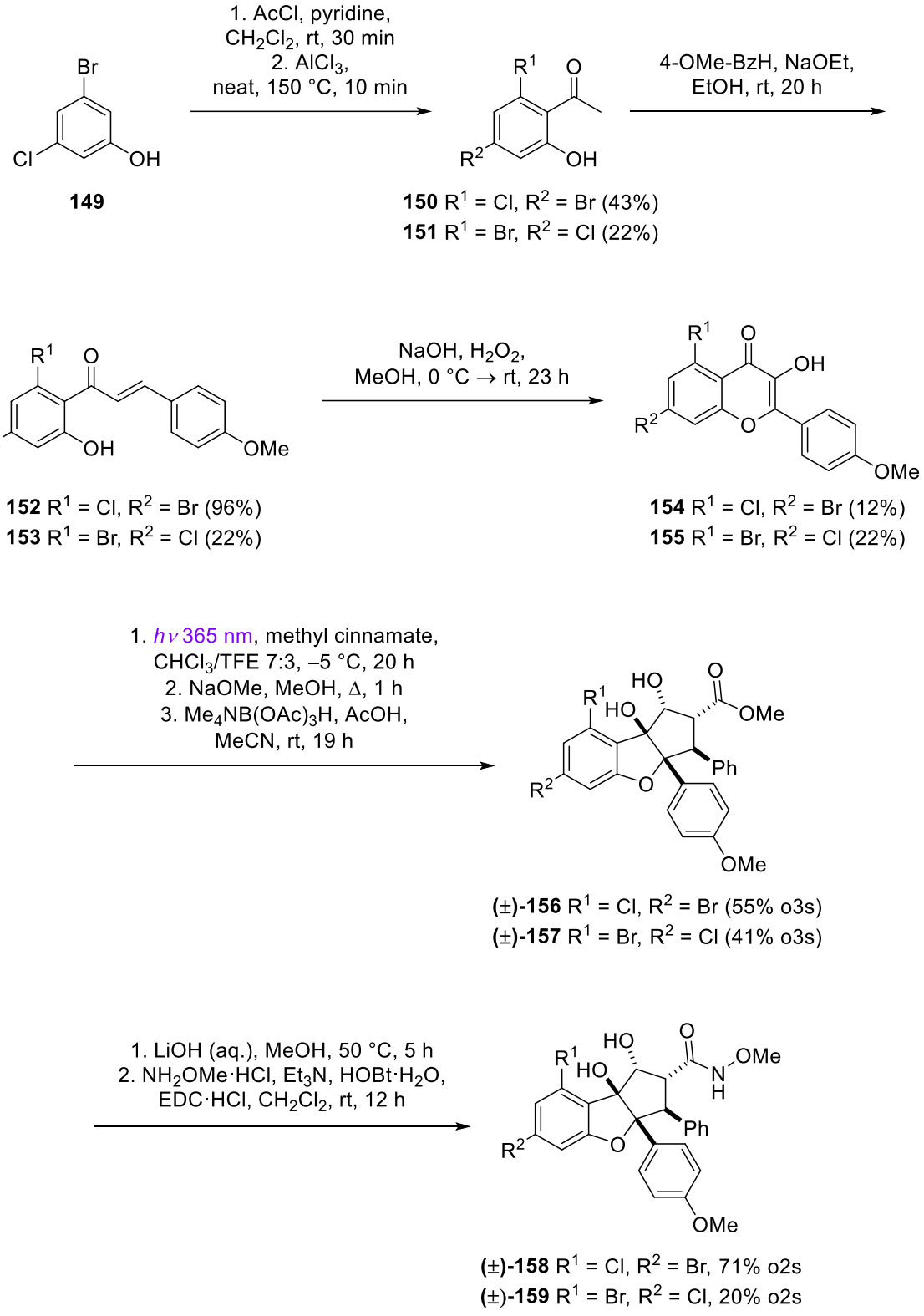
Scheme 35 Syntheses of 6,8-dihalogenated flavaglines **(±)-143**, **(±)-144** and **(±)-145**.

Inspired by the excellent antiviral activity of the 4'-brominated methyl rocaglate **(±)-145**, the synthesis of 6,8,4'-trihalogenated compound **(±)-148** was also carried out (Scheme 36). Again, the ALGAR-FLYNN-OYAMADA reaction was applied as the key step for the synthesis of flavonol **147**. Although the electron-withdrawing bromine atom was present, the yield was only slightly lower than that for the previously synthesized methoxy analogue **141**. However, the transformation sequence to flavagline **(±)-148** gave only very low yields. The reason for this may have been the extremely poor solubility of compound **147**.



Scheme 36 Synthesis of 6,8,4'-trihalogenated methyl rocaglate **(±)-148**.

Furthermore, the combination of chlorine and bromine substituents on the A ring was also to be tested. For this purpose, compounds **(±)-156** – **(±)-159** were synthesized from 3-bromo-5-chlorophenol (**149**) as shown in Scheme 37. Acetylation and FRIES rearrangement according to the previously described conditions yielded a mixture of **150** and **151** that were separable by column chromatography. Thus, the well-established synthetic route could be continued independently with both compounds. The synthesis of flavagline **(±)-157** proved to be challenging. Despite the strong structural similarities, yields were almost consistently lower than for compound **(±)-156**. However, sufficient amounts of both compounds were generated to allow conversion to *N*-methoxyamides **(±)-158** and **(±)-159**.
The di- and trihalogenated derivatives prepared were screened for their antiviral activity against HEV as well. Additionally, 6,8-difluoro methyl rocaglate **(±)-160** synthesized by VICTORIA[91] was included in the test panel. The data presented in Table 10 show that exchanging both C6 and C8 methoxy groups for a bromine has only a small effect on the activity and cytotoxicity. In the case of chlorine, a slight improvement in antiviral properties was observed. However, the cytotoxicity is significantly lower than for (±)-methyl rocaglate (**(±)-*endo*-59**). In contrast, no antiviral activity or cytotoxicity was observed for the 6,8-difluorinated compound **(±)-160**. Surprisingly, the previously demonstrated positive effect of bromine C4' position could not be detected when combined with the dichlorinated A ring. Considering the data of the mixed halogenated derivatives **(±)-156** and **(±)-157**, it became evident that bromination at C6 and chlorination at C8 positively affected the potency of the compounds, while a negative impact was observed for the opposite substitution pattern. Converting the methyl esters to the corresponding *N*-methoxyamides **(±)-158 and (±)-159** led to a positive effect in both cases, but significantly more pronounced for **(±)-159**.



149

150 R^1 = Cl, R^2 = Br (43%)
151 R^1 = Br, R^2 = Cl (22%)

152 R^1 = Cl, R^2 = Br (96%)
153 R^1 = Br, R^2 = Cl (22%)

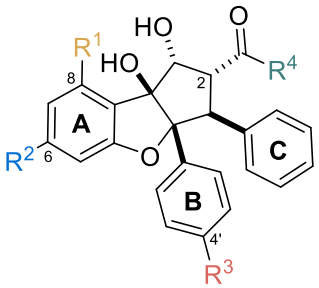
154 R^1 = Cl, R^2 = Br (12%)
155 R^1 = Br, R^2 = Cl (22%)

(±)-156 R^1 = Cl, R^2 = Br (55% o3s)
(±)-157 R^1 = Br, R^2 = Cl (41% o3s)

(±)-158 R^1 = Cl, R^2 = Br, 71% o2s
(±)-159 R^1 = Br, R^2 = Cl, 20% o2s

Scheme 37 Syntheses of 6,8-dihalogenated flavaglines **(±)-156** – **(±)-159**.

Table 10 IC_{50}, CC_{50} and SI values calculated for di- and trihalogenated rocaglates in comparison to silvestrol (**10**), (±)-methyl rocaglate (**(±)-*endo*-59**), (±)-Rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**) in HepG2.



Compound	R¹	R²	R³	R⁴	24 h IC₅₀ /nM	24 h CC₅₀ /nM	24 h SI	48 h IC₅₀ /nM	48 h CC₅₀ /nM	48 h SI
10[b]	OMe	dioxanyloxy	OMe	OMe	4.10	139	33.8	2.76	16.1	5.84
(±)-*endo*-59[a]	OMe	OMe	OMe	OMe	28.8	545	18.9	25.3	60.5	2.39
(±)-9[b]	OMe	OMe	OMe	NMe_2	29.4	494	16.8	18.3	55.1	3.01
(±)-13[b]	OMe	OMe	OMe	NH(OMe)	5.94	148	24.9	4.06	19.5	4.80
(±)-143[b]	Cl	Cl	OMe	OMe	25.2	>1000	n.d.	14.7	144	9.83
(±)-144[b]	Br	Br	OMe	OMe	37.3	647	17.4	31.0	103	3.32
(±)-145[b]	Cl	Cl	OMe	NH(OMe)	7.80	445	57.1	7.02	32.5	4.63
(±)-148[b]	Cl	Cl	Br	OMe	29.8	330	11.1	20.6	56.0	2.72
(±)-156[b]	Cl	Br	OMe	OMe	7.88	653	82.8	9.47	66.6	7.03
(±)-157[b]	Br	Cl	OMe	OMe	51.9	>1000	n.d.	40.0	108	2.70
(±)-158[b]	Cl	Br	OMe	NH(OMe)	4.71	244	51.7	3.75	15.9	4.24
(±)-159[b]	Br	Cl	OMe	NH(OMe)	3.67	347	94.6	5.26	31.1	5.91
(±)-160[b]	F	F	OMe	OMe	>1000	>1000	n.d.	>1000	>1000	n.d.

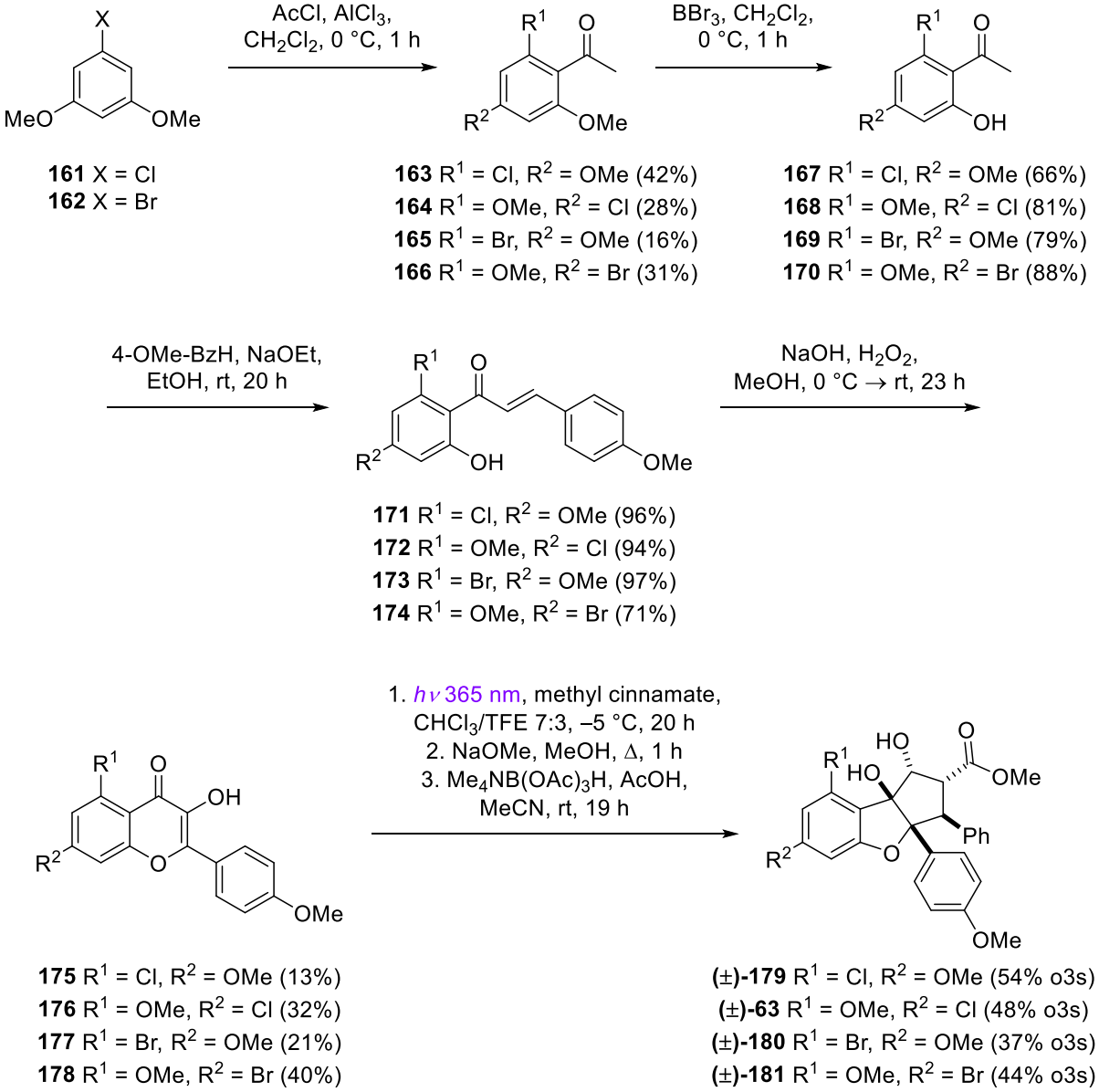
Mean values from multiple determinations ([a] $n = 2$; [b] $n = 3$)

From these data, it could be concluded that there are significant differences between the C6 and C8 positions with respect to the effect of halogenation. Bromination at C6 position seemed to lead to a significant enhancement in antiviral activity, whereas this positive impact was apparently counterbalanced by a bromine atom at C8. In contrast, for the 8-chloro derivatives, the negative effect was either absent or much less pronounced. Interestingly, it was generally observed that the cytotoxicity of the 6,8-dihalogenated derivatives was reduced compared to their 6,8-dimethoxy analogues although exhibiting similar or even increased activity.

From these conclusions, the question arose whether the effects on activity and cytotoxicity resulted from the substitution of both methoxy groups or whether the respective effects originated only in the halogenation of one of the two positions. To address this question, the 6- and 8-mono-chlorinated and brominated methyl rocaglates were synthesized as well (Scheme 38). Similar to the case of the mixed-halogenated flavaglines **(±)-156** and **(±)-157**, the fact that the acetylation of 1-chloro-3,5-dimethoxybenzene (**161**) and 1-bromo-3,5-dimethoxybenzene (**162**) proceeded in a non-regioselective manner was turned to advantage. FRIEDEL-CRAFTS acylation carried out according to a protocol by CAI

and co-workers[108] employing substrate **161** gave preferentially *ortho*-chloro acetophenone **163**, while the reaction using **162** led primarily to *para*-bromo acetophenone **166**, probably due to the higher steric demand of the bromine.

Selective demethylation in *ortho* position and subsequent chalcone formation proceeded in good to excellent yields in all cases. Surprisingly, the ALGAR-FLYNN-OYAMADA reaction gave better results for the 4'-halogenated compounds **172** and **174** than for the 2'-halogenated ones **171** and **173**, although the later featured an electron withdrawing group in *ortho* position (c.f. Section A3.2). A plausible explanation would be that the *para*-halo substituent, similar to the nitrogen atom of the pyridine in Scheme 17, compensated for the electron-donating properties of the methoxy group and thus ensured the 6-*endo-trig* cyclization to be preferred. In the case of the *ortho*-halogenated chalcones, on the other hand, the increased steric demand most likely led to lower yields. However, all four flavonols **175** – **178** were prepared in sufficient amounts to successfully carry out the synthesis of the mono-halogenated flavaglines **(±)-63** and **(±)-179** – **(±)-181** by the well-known three-step procedure.

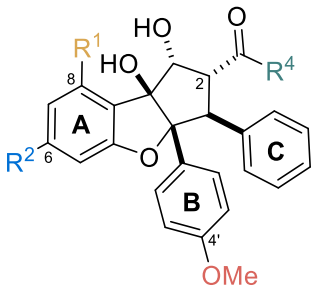


Scheme 38 Syntheses of 6- and 8-monohalogenated flavaglines **(±)-63** and **(±)-179** – **(±)-181**.

The final antiviral tests also included the 6- and 8-fluro rocaglates **(±)-182** and **(±)-183** synthesized by VICTORIA.[91] The results, listed in Table 11, indicated that the substitution at C6 position by a chlorine or bromine resulted in a superior enhancing effect on the activity, whereas 6-fluorinated derivative **(±)-185** was hardly active in the antiviral assay. Interestingly, the increase in activity was accompanied by only a minor rise in cytotoxicity. Although being racemic mixtures, **(±)-63** and **(±)-181** were about as potent as (–)-silvestrol **10**, but showed a significantly reduced cytotoxic effect.

Halogenation at C8, on the other hand, resulted in a deterioration of the IC_{50} values by a factor of about two to three in all cases compared to their 8-methoxy analogues. In the case of 8-chlorinated and 8-brominated analogues **(±)-179** and **(±)-180** this might be due to steric interactions with the enzyme or eIF4A. A more plausible explanation, which also incorporates the reduced activity of the 8-fluoro flavagline **(±)-182**, arises from the work of REICH's group. They found through DFT calculations that the natural methoxy group at the C6 position forms an intramolecular hydrogen bond with the secondary alcohol at C1. This leads to a fixed torsion angle between the B- and C-phenyl rings and thus to an optimized positioning within the active pocket.[67] Although halogen atoms can also act as hydrogen bond acceptors, the bonds formed are comparatively weak, which probably explains the reduced activity.[109]

Table 11 IC_{50}, CC_{50} and SI values calculated for mono-halogenated rocaglates **(±)-63 and (±)-179 – (±)-183** in comparison to silvestrol (**10**), (±)-methyl rocaglate (**(±)-*endo*-59**), (±)-Rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**) in HepG2.



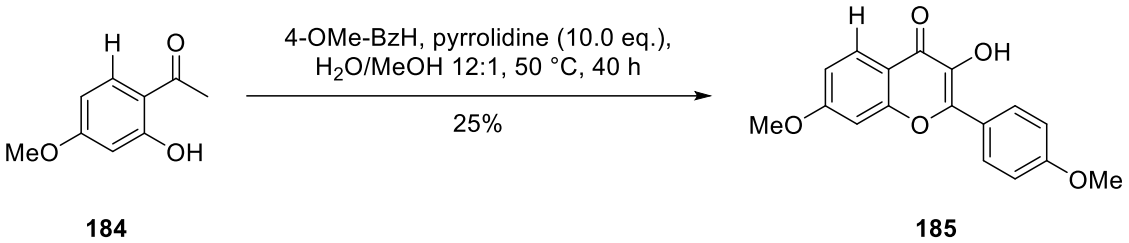
Compound	R¹	R²	R⁴	24 h IC₅₀ /nM	24 h CC₅₀ /nM	24 h SI	48 h IC₅₀ /nM	48 h CC₅₀ /nM	48 h SI
10[b]	OMe	dioxanyloxy	OMe	4.10	139	33.8	2.76	16.1	5.84
(±)-*endo*-59[a]	OMe	OMe	OMe	28.8	545	18.9	25.3	60.5	2.39
(±)-9[b]	OMe	OMe	NMe_2	29.4	494	16.8	18.3	55.1	3.01
(±)-13[b]	OMe	OMe	NH(OMe)	5.94	148	24.9	4.06	19.5	4.80
(±)-179[b]	Cl	OMe	OMe	92.7	990	10.7	76.3	161	2.11
(±)-63[b]	OMe	Cl	OMe	5.44	341	62.7	2.97	25.1	8.45
(±)-180[b]	Br	OMe	OMe	86.5	946	10.9	52.1	129	2.47
(±)-181[b]	OMe	Br	OMe	3.07	183	59.5	1.47	15.1	10.3
(±)-182[b]	F	OMe	NH(OMe)	16.9	437	25.9	12.7	44.0	3.47
(±)-183[b]	OMe	F	OMe	>1000	>1000	n.d.	732	980	1.34

Mean values from multiple determinations ([a] $n = 2$; [b] $n = 3$)

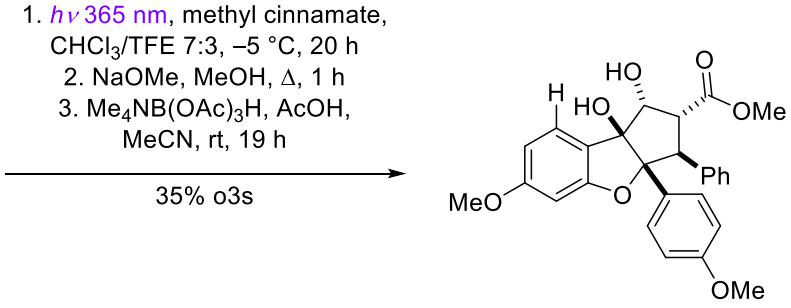
A3.6 Synthesis of Further C8-Modified Flavaglines

To further support the hypothesis that the hydrogen bond-accepting character is crucial rather than the steric demand in the selection of the substituent at C8 position, two additional flavaglines were synthesized. Both derivatives lacked a hydrogen bond acceptor at C8. In addition, the substituents at this position were smaller than in all flavaglines synthesized previously in this work.

The first target was the derivative **(±)-186** unsubstituted at C8, which was prepared as shown in Scheme 39 in only four steps starting from commercially available 2'-hydroxy-4'-methoxyacetophenone (**184**). In the initial step, flavonol **185** was obtained in 25% yield by the pyrrolidine-mediated one-pot reaction presented in Section A3.2.



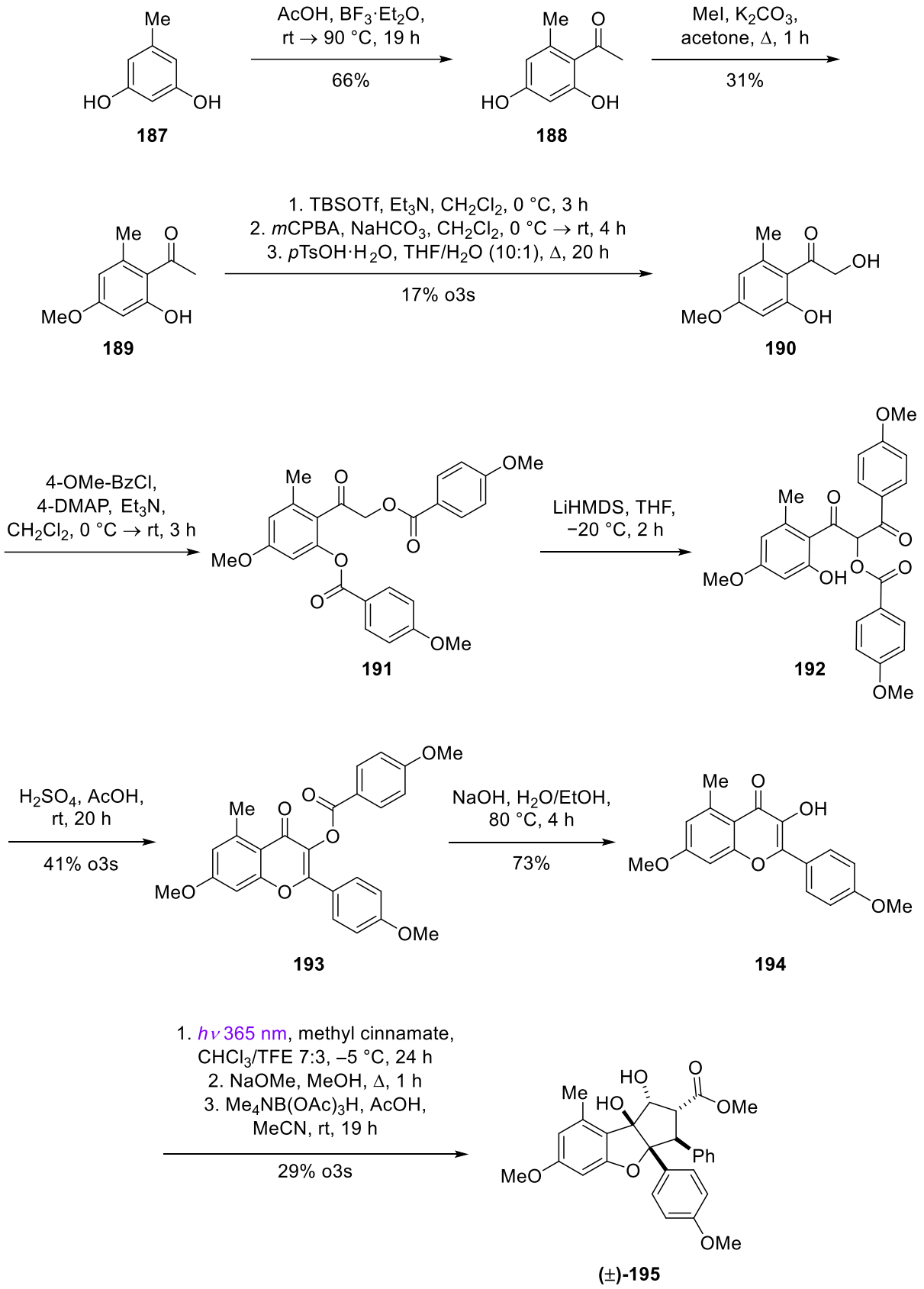
184 **185**



(±)-186

Scheme 39 Synthesis of flavagline **(±)-186**.

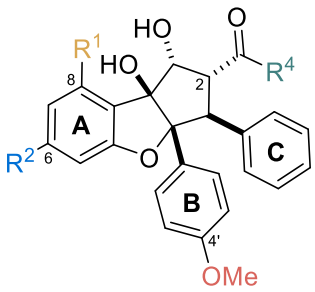
The second compound was 8-methyl analogue **(±)-195**, which was synthesized starting from orcinol (**189**). In this case, the BAKER-VENKATARAMAN synthesis was utilized (Scheme 40). Strikingly, for this derivative the yield in almost every step was lower than for the flavaglines previously synthesized via this route.



Scheme 40 Synthesis of 8-methyl flavagline **(±)-195**.

Finally, these two derivatives were also tested for their antiviral activity against HEV and their cytotoxicity. Compared to (±)-methyl rocaglate **((±)-*endo*-59),** both compounds showed IC_{50} values approximately ten times higher. However, cytotoxicity did not decrease to the same extent, with compound **(±)-188** also being significantly more cytotoxic than **(±)-195**. These results supported the hypothesis that a hydrogen bond acceptor at C8 position is an important structural feature of the flavaglines, since compounds **(±)-186** and **(±)-195** are even less active compared to the C8-halogenated derivatives such as **(±)-179** and **(±)-180** (Table 12), which might be able to form weak hydrogen bonds to the secondary alcohol.

Table 12 IC_{50}, CC_{50}, SI values calculated for C8-modified rocaglates in comparison to silvestrol (**10**), (±)-methyl rocaglate (**(±)-*endo*-59**), (±)-Rocaglamide (**(±)-9**) and (±)-CR-31-B (**(±)-13**) in HepG2.



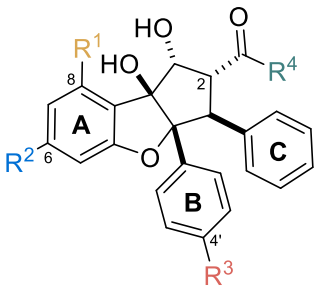
Compound	R^1	R^2	R^4	24 h			48 h		
				IC_{50} /nM	CC_{50} /nM	SI	IC_{50} /nM	CC_{50} /nM	SI
10[b]	OMe	dioxanyloxy	OMe	4.10	139	33.8	2.76	16.1	5.84
(±)-*endo*-59[a]	OMe	OMe	OMe	28.8	545	18.9	25.3	60.5	2.39
(±)-9[b]	OMe	OMe	NMe_2	29.4	494	16.8	18.3	55.1	3.01
(±)-13[b]	OMe	OMe	NH(OMe)	5.94	148	24.9	4.06	19.5	4.80
(±)-179[b]	Cl	OMe	OMe	92.7	990	10.7	76.3	161	2.11
(±)-180[b]	Br	OMe	OMe	86.5	946	10.9	52.1	129	2.47
(±)-186[b]	OMe	H	OMe	229	986	4.31	301	249	0.83
(±)-195[b]	OMe	Me	OMe	213	>1000	n.d.	282	379	1.34

mean values from multiple determinations ([a] $n = 2$; [b] $n = 3$)

A4 Conclusions and Future Work

Within this sub-project of the present dissertation, a total number of 40 silvestrol respectively rocaglamide derivatives were synthesized. Out of these, 27 were tested for their antiviral properties against hepatitis E and their cytotoxicity in Hep2G cells by collaborators at the Ruhr-University Bochum. Some of the compounds have been reported in literature before. These confirmed that the previously reported SAR data, derived predominantly from studies in cancer research, are also applicable to the antiviral properties of flavaglines. In addition, five derivatives synthesized by VICTORIA and an authentic sample of the natural compound silvestrol (**10**) were included in the test series. The results are summarized in Table 13.

Table 13 IC_{50}, CC_{50} and SI values calculated for all flavaglines synthesized as part of this project in comparison to silvestrol (**10**) in HepG2.



Compound	R¹	R²	R³	R⁴	24 h IC₅₀ /nM	24 h CC₅₀ /nM	24 h SI	48 h IC₅₀ /nM	48 h CC₅₀ /nM	48 h SI
10[b]	OMe	dioxanyloxy	OMe	OMe	4.10	139	33.8	2.76	16.1	5.84
(±)-*endo*-59[a]	OMe	OMe	OMe	OMe	28.8	545	18.9	25.3	60.5	2.39
(±)-9[b]	OMe	OMe	OMe	NMe_2	29.4	494	16.8	18.3	55.1	3.01
(±)-13[b]	OMe	OMe	OMe	NH(OMe)	5.94	148	24.9	4.06	19.5	4.80
(±)-*endo*-103[a]	OMe	OBn	OMe	OMe	437	>1000	n.d.	413	453	1.10
(±)-*exo*-103[a]	OMe	OBn	OMe	OMe	>1000	>1000	n.d.	>1000	>1000	n.d.
(±)-118[a]	OMe	OMOM	OMe	NH(OMe)	10.4	268	25.7	5.86	22.3	3.80
(±)-119[a]	OMe	OTf	OMe	OMe	361	>1000	n.d.	377	468	1.24
(±)-62[a]	OMe	CN	OMe	OMe	3.58	162	45.3	3.39	10.7	3.16
(±)-121[a]	OMe	$-CO_2CH_2CF_3$	OMe	OMe	18.1	311	17.2	13.2	41.0	3.11
(±)-125[a]	OMe	$-CO_2(CH_2)_3OH$	OMe	OMe	7.71	132	17.1	6.18	15.4	2.50
(±)-126[a]	OMe	$-CO_2CH_2CF_2CH_2OH$	OMe	OMe	6.04	178	29.6	4.51	12.7	2.81
(±)-127[a]	OMe	$-CO_2(CH_2)_3NH_2{\cdot}TFA$	OMe	OMe	4.20	144	32.2	4.35	19.8	4.56
(±)-134[b]	OMe	OMe	Br	OMe	7.18	289	40.3	9.87	31.9	3.23
(±)-135[b]	OMe	OMe	Cl	OMe	19.5	400	20.6	16.3	45.7	2.80
(±)-136[b]	OMe	OMe	F	OMe	338	>1000	n.d.	266	440	1.65
(±)-143[b]	Cl	Cl	OMe	OMe	25.2	>1000	n.d.	14.7	144	9.83
(±)-144[b]	Br	Br	OMe	OMe	37.3	647	17.4	31.0	103	3.32

(±)-145[b]	Cl	Cl	OMe	NH(OMe)	7.80	445	57.1	7.02	32.5	4.63
(±)-148[b]	Cl	Cl	Br	OMe	29.8	330	11.1	20.6	56.0	2.72
(±)-156[b]	Cl	Br	OMe	OMe	7.88	653	82.8	9.47	66.6	7.03
(±)-157[b]	Br	Cl	OMe	OMe	51.9	>1000	n.d.	40.0	108	2.70
(±)-158[b]	Cl	Br	OMe	NH(OMe)	4.71	244	51.7	3.75	15.9	4.24
(±)-159[b]	Br	Cl	OMe	NH(OMe)	3.67	347	94.6	5.26	31.1	5.91
(±)-160[b]	F	F	OMe	OMe	>1000	>1000	n.d.	>1000	>1000	n.d.
(±)-179[b]	Cl	OMe	OMe	OMe	92.7	990	10.7	76.3	161	2.11
(±)-63[b]	OMe	Cl	OMe	OMe	5.44	341	62.7	2.97	25.1	8.45
(±)-180[b]	Br	OMe	OMe	OMe	86.5	946	10.9	52.1	129	2.47
(±)-181[b]	OMe	Br	OMe	OMe	3.07	183	59.5	1.47	15.1	10.3
(±)-182[b]	F	OMe	OMe	NH(OMe)	16.9	437	25.9	12.7	44.0	3.47
(±)-183[b]	OMe	F	OMe	OMe	>1000	>1000	n.d.	732	980	1.34
(±)-186[b]	H	OMe	OMe	OMe	229	986	4.31	301	249	0.83
(±)-195[b]	Me	OMe	OMe	OMe	213	>1000	n.d.	282	379	1.34

mean values from multiple determinations ([a] $n = 2$; [b] $n = 3$)

All flavaglines synthesized were tested as racemic mixtures. For technical and time reasons, the intended racemic resolution by chiral HPLC was not carried out. However, the separation of the enantiomers was successfully demonstrated on the basis of benzyl ether **(±)-*endo*-103**. However, even in the racemic form, the frontrunners nitrile **(±)-62**, ester **(±)-127**, the 6,8-dihalogenated CR-31-B analogues **(±)-158** and **(±)-159** as well as bromide **(±)-181** exhibit antiviral activities comparable to that of the enantiomerically pure silvestrol (**10**).

In addition, a whole set of structure-activity relationships could also be identified from these results, as depicted in Figure 15.

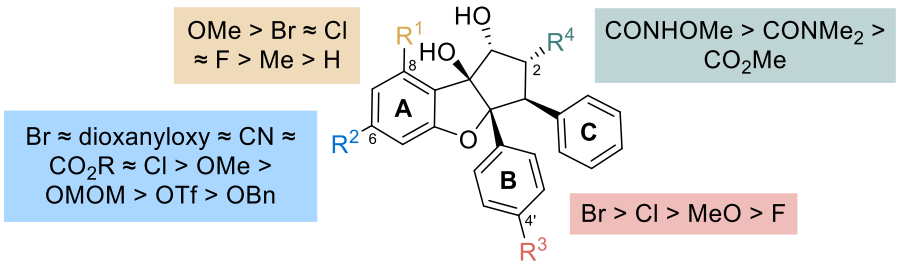


Figure 15 Summary of structure-activity relationships of flavaglines identified from the results of this thesis.

In the C6 position, the substitution of the methoxy group by the (pseudo)halides chlorine, bromine or cyanide proved to be most advantageous. The installation of an ester also led to a significant increase in antiviral activity. Especially in combination with a terminal hydrogen bond donor, highly potent compounds could be obtained. On the other hand, a fluorine atom as well as a triflate group lower the activity, as did benzyl and methoxymethyl ethers. Overall, the antiviral activity of the derivatives was found to correlate neither with the steric claim nor with the electronic properties of the C6 substituents.

It is therefore plausible that an intermolecular interaction with the RNA or enzyme, which has not yet been described in literature, is responsible for the significant differences in potency of the derivatives modified at C6 position. Computational methods could be applied to model the positioning of the synthesized derivatives within the enzyme-RNA pocket to identify the attractive interactions. Likewise, the hypothesis that the esters **(±)-125** – **(±)-127** bind with their terminal hydrogen bond donor to an acceptor within the arginine pocket of eIF4A might be verified by *in silico* methods.

Further potential target structures (Figure 16) modified at C6 position also arises primarily from the promising results of the carboxylic acid esters. In particular, synthesis of analogues with shortened or extended chains could reveal whether a particular chain length geometrically best mimic the dioxanyloxy unit of silvestrol. Similarly, various functionalization at the terminal position could be explored. While enhancing the hydrogen bond donor character could improve the affinity to the enzyme, it could also increase the interaction with surrounding water molecules, which possibly might reduce the attractive interactions with the arginine pocket. Furthermore, esters are susceptible to hydrolysis, rendering them as not a well-suited structural feature for drug candidates. Therefore, future work should also focus on carboxylate ester isosteres. Heterocycles are particularly suitable for this purpose. However, this would decrease the degrees of freedom of the alkyl chain, which might hinder the alignment of the terminal group to the binding acceptor of the enzyme.

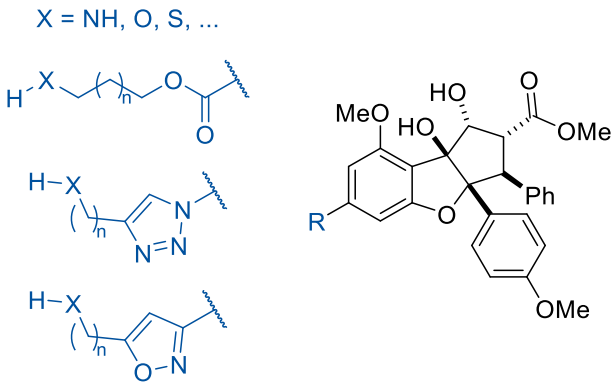


Figure 16 Potential future target structures mimicking the dioxanyloxy unit.

In C8 position, the overall results are completely different. Any modification at this position resulted in significantly less potent derivatives. In particular, in the absence of a hydrogen bond acceptor at this position, antiviral activity noticeably dropped. According to the results of REICH *et al.*, the methoxy group in this position is essential for fixing the conformation of the cyclopenta[*b*]benzofuran core and, as a consequence, the torsion angle between the B and C rings.[67]

Further studies should therefore test the influence of stronger hydrogen bond acceptors at this position, such as thioesters or carbonyl substituents.

The syntheses of derivatives halogenated in the C4' position led to the hypothesis that substituents with a higher steric demand are advantageous. However, future work is needed to verify this assumption. Similar to the C6 position, 4'-bromo rocaglate **(±)-134** could be utilized for late modifications via palladium-catalyzed cross-coupling reactions to investigate the influence of additional substituents.

Lastly, the synthesis of derivatives featuring a methyl ester, dimethylamide or *N*-methoxyamides at C2 confirmed the literature-known trend. In all cases, the *N*-methoxyamides were significantly more

active than the corresponding methyl ester and dimethylamide. However, this effect differed significantly across derivatives, but no obvious relationship with other structural motifs was found.

With regard to cytotoxicity, it shows clear correlation to the antiviral activity. However, when IC_{50} values were plotted against the selectivity indices (Figure 17), it became evident that no linear correlation was present. The most potent derivatives were often significantly less cytotoxic relative to their activity. A potential explanation for this could lie on cytotoxic metabolites formed from the flavaglines irrespective of the substitution pattern. Alternatively, an unidentified off-target could be contributing to the cytotoxic properties of the tested compounds.

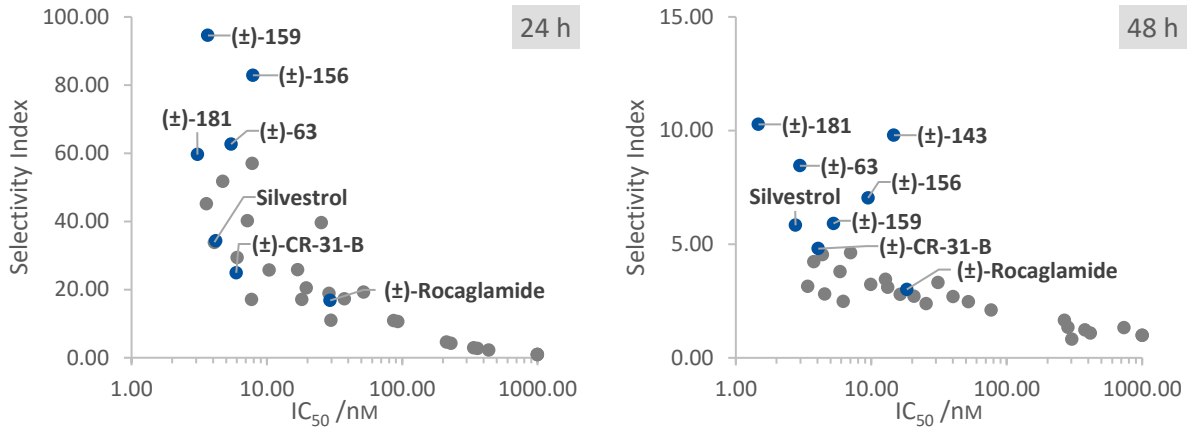
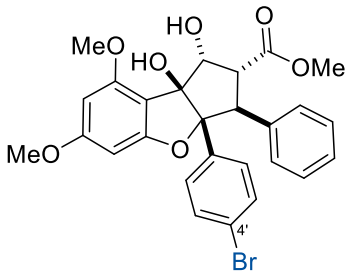


Figure 17 Plots of SI against IC_{50} calculated for the synthesized derivatives and silvestrol (**10**) after 24 h and 48 h in Hep2G cells; selected promising candidates and reference substances are highlighted in blue.

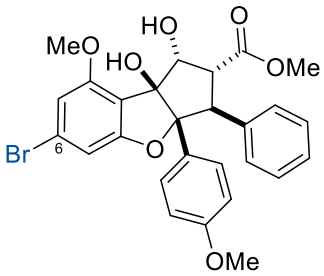
Interestingly, while some modifications appear to have a major impact on antiviral activity, they seem to affect cytotoxicity only to a minor extent. In particular, C6-chlorinated and -brominated compounds **(±)-63** and **(±)-181** were noteworthy here as they are among the most potent candidates but exhibit comparatively low cytotoxicity. The same applies to the compounds featuring an *N*-methoxyamide at C2 position. Each of them exhibits better selectivity indices compared to their corresponding methyl esters. An obvious next step would therefore be the synthesis of the corresponding *N*-methoxyamide analogues of compounds **(±)-63** and **(±)-181**, which are expected not only to be more potent but also to have the advantage of improved selectivities.

In contrast, incorporation of an ester at C6 resulted in lower SI values, possibly due to their susceptibility to hydrolysis, which could lead to the formation of potentially toxic alcohols. However, it is less easy to explain why modifications at the C4' position had a negative impact on the selectivity indices. For example, comparing 4'-bromo rocaglate **(±)-134** with 6-bromo rocaglate **(±)-181** (Table 14), it becomes apparent that bromination at C6 resulted in a more effective but also more selective drug candidate.

Table 14 IC_{50}, CC_{50} and SI values calculated for **(±)-134** and **(±)-181** in HepG2.



(±)-134



(±)-181

Compound	24 h			48 h		
	IC_{50} /nM	**CC_{50} /nM**	**SI**	**IC_{50} /nM**	**CC_{50} /nM**	**SI**
(±)-134[a]	7.18	289	40.3	9.87	31.9	3.23
(±)-181[a]	3.07	183	59.5	1.47	15.1	10.3

[a] Mean values from multiple determinations (*n = 3*)

Future work should therefore elucidate more precisely which modifications are beneficial with regard to utilization as an antiviral drug. Since several of the compounds are already active at low nanomolar concentrations, the focus should now be on minimizing toxicity. Another important issue that was not addressed in this work was the optimization of drug-like properties, such as solubility, permeability, metabolic stability, and transporter effects.

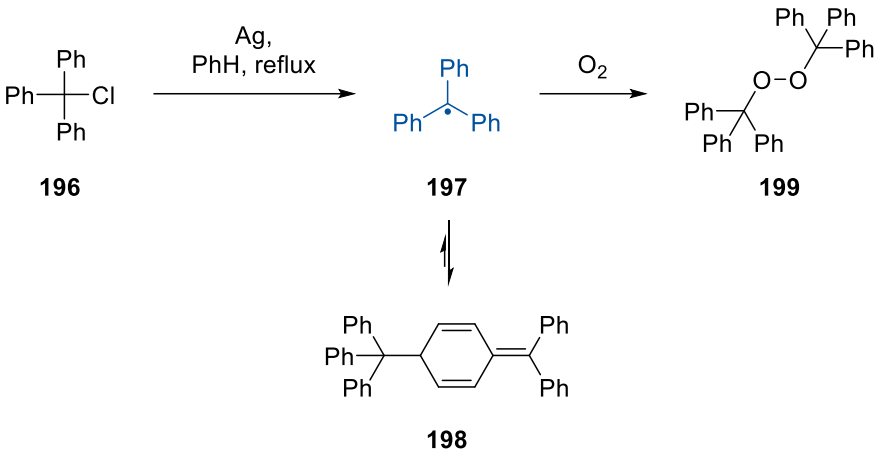
Topic B: Development of Novel Methodologies in the Field of Radical Chemistry

B1 Introduction

B1.1 History of Free Radicals in Organic Synthesis

As reactive intermediates, free radicals play an important role in modern organic synthesis. Single-electron transfers are the fundamental processes behind modern methodologies such as photoredox catalysis or electrochemistry. Since the first publication of the KOLBE electrolysis in 1848, radical reactions became part of the synthetic chemist's repertoire.[110] However, the existence of free radicals was still completely unknown to the chemists of the time. Even many decades later, this class of compounds was regarded more as a structural curiosity rather than a productive and applicable area of research.[111]

The first organic radical was discovered by GOMBERG in 1900. In an attempt to synthesize hexaphenylethane through a WURTZ coupling of triphenylmethyl chloride **(196)**, he obtained a yellow solution of the persistent triphenylmethyl radical (**197**) and its dimer **198** in an equilibrium state (Scheme 41). While the solution was stable under a carbon dioxide atmosphere, precipitation of a colorless solid was observed when exposed to air. The precipitate was identified as peroxide **199**, leading to the conclusion that it was formed by trapping two triphenylmethyl radicals (**197**) with atmospheric oxygen.[112] Although GOMBERG ended his paper with the sentence, "This work will be continued and I wish to reserve the field for myself", fortunately other chemists did not follow this request and developed the field of radical chemistry to its present state.



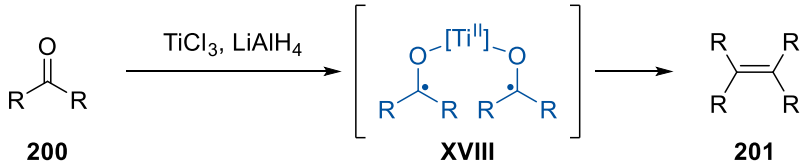
Scheme 41 GOMBERG's experiment revealing the existence of organic free radical **197**.

The development of radical chemistry proceeded sluggishly in the first decades. It took almost 30 years until PANETH and HOFEDITZ succeeded in proving the possibility of methyl radicals to exist in the gas phase for short periods of time.[113]

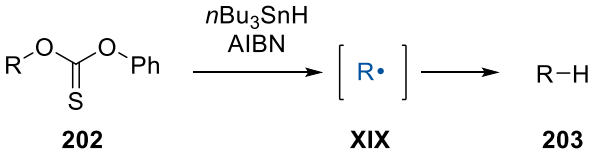
The important role of radicals as reaction intermediates in solution was first addressed in 1937. In their article in Chemical Reviews, HEY and WATERS proposed mechanisms involving radical key intermediates for a large number of organic reactions. In this publication, they also established the notation of marking radicals with a single dot representing an unpaired electron.[114] Another milestone in the field of radical chemistry was the development of electron paramagnetic resonance spectroscopy (EPR) in 1944, which allows the detection of intermediate radicals in solution and the elucidation of their structure.[115]

However, the "free radical hypothesis" was not generally accepted until the 1950s.[116] This changed with numerous organic and physicochemical studies that shed light on radical mechanisms of numerous reactions and opened path to the successful application of radical chemistry in organic synthesis. In the 1970s and 1980s, pioneering methodologies were developed that are still utilized in modern synthetic chemistry.[117,118] These include the McMurry coupling,[119] the Barton-McCombie deoxygenation,[120] the Barton decarboxylation[121] and the Giese reductive addition[122] (Scheme 42).

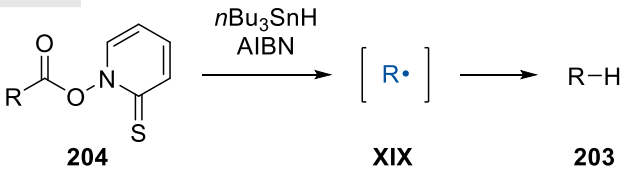
McMurry coupling (1974)



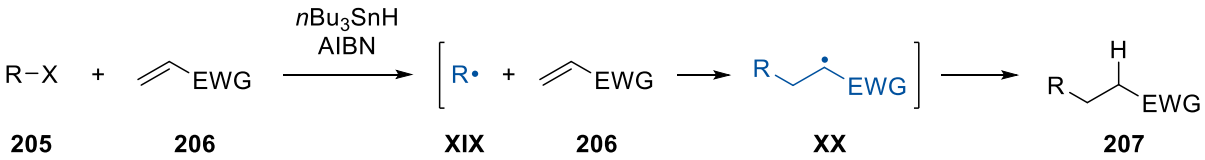
Barton-McCombie deoxygenation (1975)



Barton decarboxylation (1983)

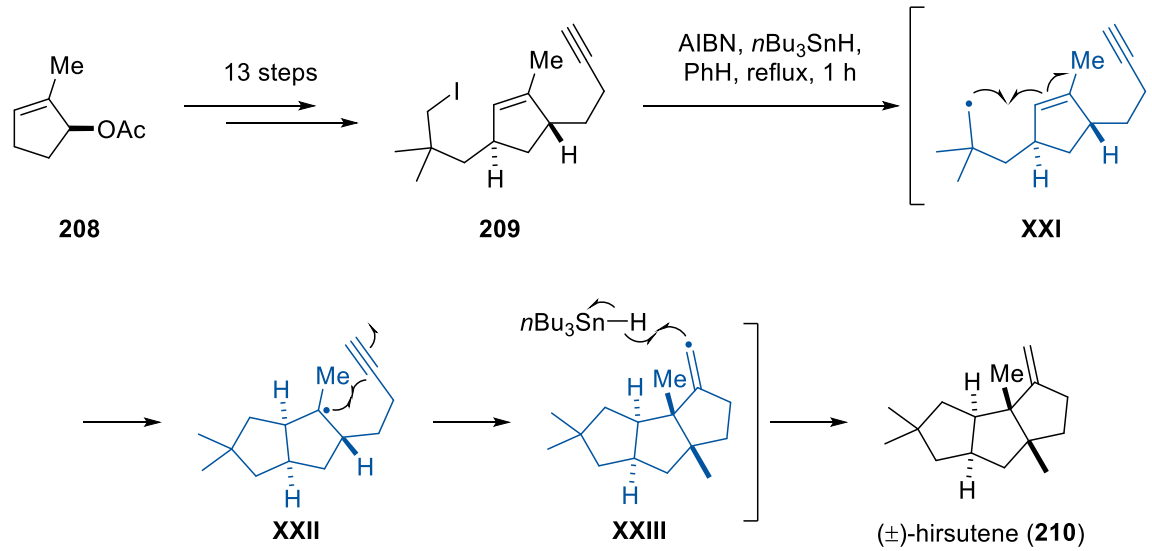


Giese reductive addition (1984)



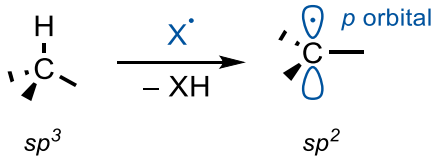
Scheme 42 Pioneering organic name reactions in the field of radical chemistry.

This period also saw the development of the first natural product syntheses, which were deliberately based on the still young single-electron chemistry. An impressive example is the total synthesis of (±)-hirsutene (**210**) by Curran in 1985.[123] In the final step of the synthesis, the 5,5,5-tricyclic fused ring system is assembled by a tandem radical cyclization from iodide **209** initiated by azobisisobutyronitrile (AIBN) and tributyltin hydride (Scheme 43).



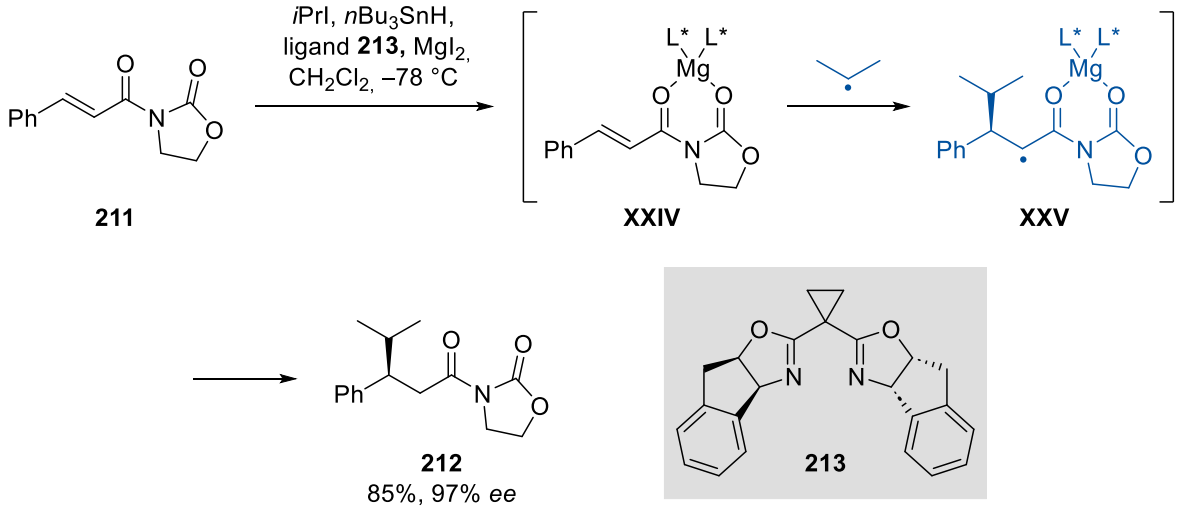
Scheme 43 Total synthesis of (±)-hirsutene (**210**) by CURRAN *et al.* via a radical cyclization.[123]

Before the turn of the millennium, another major problem in radical chemistry was addressed. During the formation of an alkyl radical, the hybridization of the carbon changes from sp^3 to sp^2. The consequence is the loss of stereochemical information (Scheme 44).



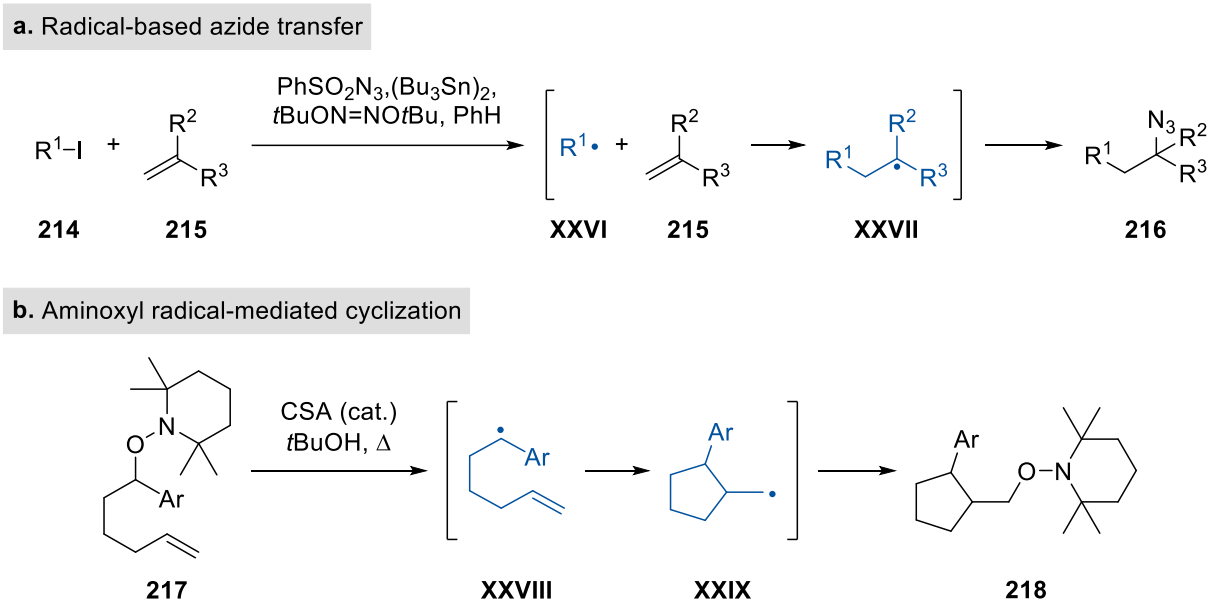
Scheme 44 Formation of an alkyl radical leads to the loss of stereochemical information.

Therefore, stereocontrolled radical reactions have always posed a challenge that has been elegantly tackled by the pioneering works of CURRAN, GIESE, PORTER, SIBI and RENAUD.[117,124,125] A prominent example is the enantioselective addition of alkyl radicals to oxazolidinone imides using a combination of a LEWIS acid and a chiral bis(oxazoline) ligand (Scheme 45).[125]



Scheme 45 Enantioselective radical addition mediated by a LEWIS acid and a chiral bis(oxazoline) ligand **213**.[125]

In the early 2000s, RENAUD has also been influential in establishing radical-based azide transfer as a method for the formation of C–N bonds in highly efficient and selective manner (Scheme 46a).[126,127] Around the same time, STUDER was able to accomplish major breakthroughs in the control of radical polymerizations and cyclizations through his work on aminoxyl radicals (Scheme 46b).[128,129,130][131]

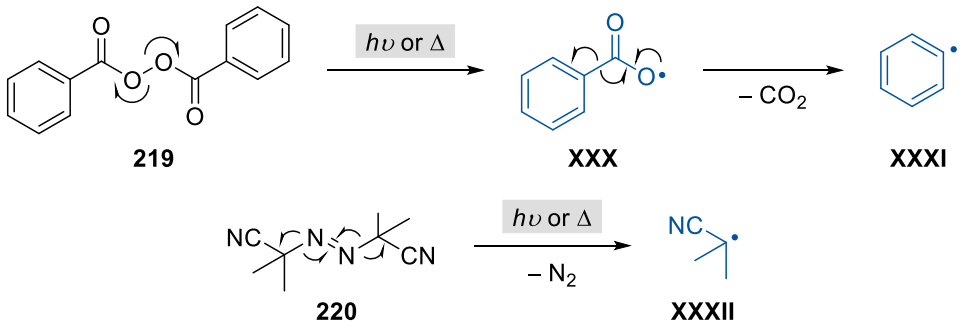


Scheme 46 a. Radical-based azide transfer developed by RENAUD;[127] **b.** Aminoxyl radical-mediated cyclization by STUDER.[129]

Over the past 20 years, radical chemistry has experienced a renaissance resulting in the development of innumerable elegant total syntheses.[111] In particular, the use of radical cross-coupling reactions has in several cases opened up much more efficient synthetic pathways than those achievable by two-electron chemistry.[132]

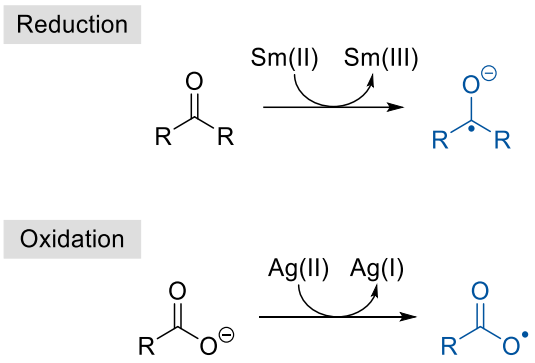
B1.2 General Chemistry of Radicals

The most common way to generate radicals is homolytic cleavage of covalent bonds. To break the two-electron bond, energetic impact exceeding the bond dissociation energy is required. Classic initiators for radical processes are benzoyl peroxide (**219**) or AIBN (**220**), which feature very readily cleavable bonds. Upon thermally or photolytically induced dissociation, the compounds dissociate to give radical **XXX** and **XXXII**, respectively. Carboxyl radical **XXX** immediately undergoes decarboxylation to give phenyl radical (**XXXI**) (Scheme 47).[116,133]



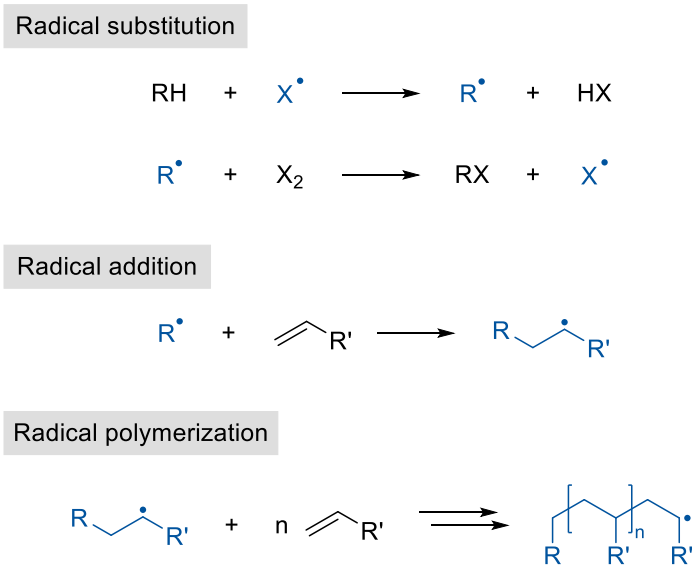
Scheme 47 Generation of radicals by the homolytical cleavage of covalent bonds.

In addition, radicals can be generated by redox processes involving the transfer of a single electron. Representative examples are the reduction of a ketone by samarium(II) iodide to yield a ketyl radical and the oxidation of a carboxylate by a Ag(II) species to generate a carboxyl radical (Scheme 48).[134]



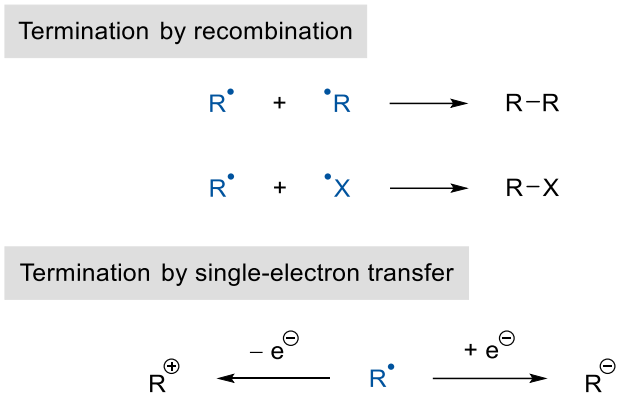
Scheme 48 Generation of radicals by redox systems.[134]

The formation of a radical species can initiate radical chain propagation. In this process, the radical reacts with a molecule to generate a new radical species. These are typically addition and substitution reactions (Scheme 49). In theory, this process can be repeated an infinite number of times, which is the basic principle of radical polymerization. The difference in bond dissociation energies of starting materials and products is the major driving force of the process and determines the progression of radical chain reactions.[135]



Scheme 49 Radical chain propagation reactions.[134,135]

Finally, the termination of the chain propagation can occur by the combination of two radicals to form a stable, spin-paired product (Scheme 50). This process is thermodynamically favorable, but due to the typically low concentration of the radical species in the reaction mixture, the probability of two radicals colliding is rather low. Alternatively, as in the case of initiation, oxidative or reductive single-electron transfer reactions are also conceivable for the termination of radical chain propagation.[134]



Scheme 50 Termination of radical chain reactions.[116]

B1.3 Radical Stability and Philicity

A major factor controlling radical reactions is the stability of the radical species. Because of the unpaired electron, in the vast majority of cases radicals are stable for only fractions of a second and rapidly undergo transformations to generate a more stable product. However, there are some examples of compounds containing an unpaired electron that exhibit comparatively high stability. The GOMBERG radical (**197,** Figure 18) described in Section B1.1 forms in solution under an inert atmosphere a stable equilibrium with its dimer **198** (Scheme 41) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, **221**) can be kept even as a pure samples for years.

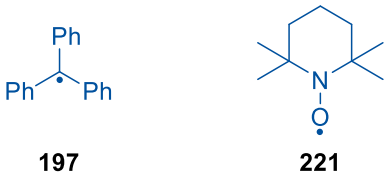
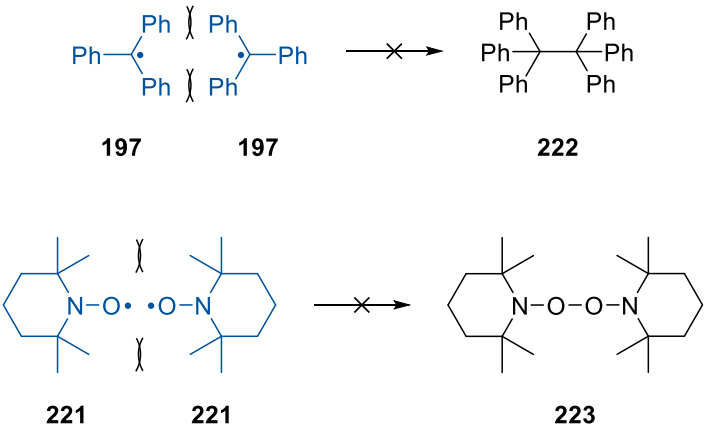


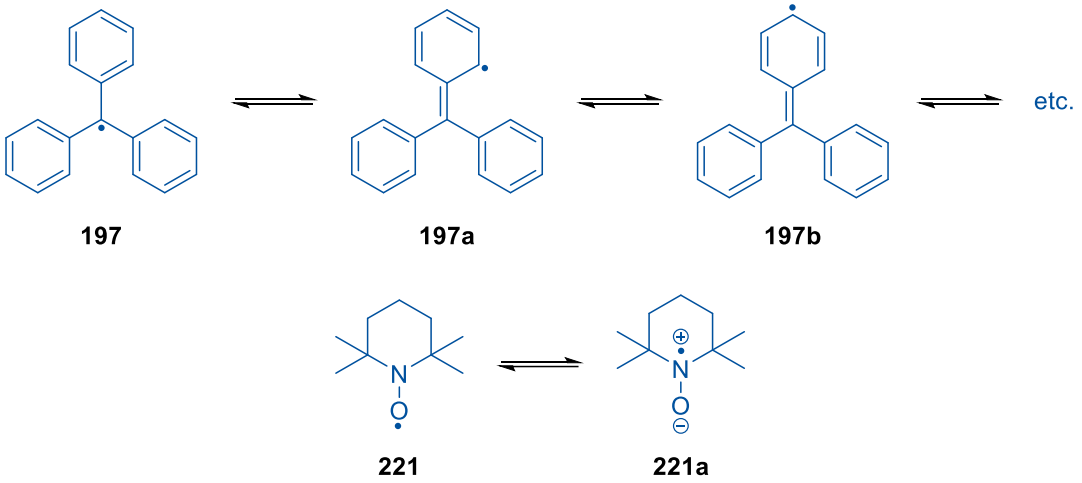
Figure 18 Structures of the GOMBERG radical (**197**) and TEMPO (**221**).

These exceptional properties can be explained by kinetic and thermodynamic effects. Kinetic stabilization arises from steric hindrance of substituents adjacent to the radical, which hampers dimerization (Scheme 51) and reduces the reactivity of the radical. However, since radicals are generally extremely reactive, it is not possible to stabilize them by steric effects only.[135]



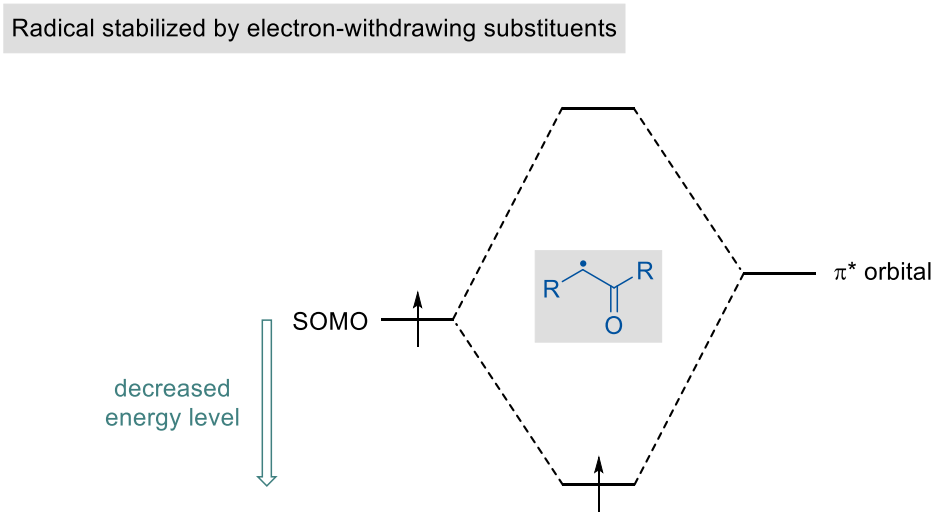
Scheme 51 Steric hindrance hampers dimerization of the GOMBERG radical (**197**) and TEMPO (**221**).

Thermodynamic effects have a significantly stronger impact and can be attributed mainly to resonance stabilization caused by the delocalization of the unpaired electron. For example, the GOMBERG radical can be represented in several contributing structures **197**-**197b** in which the spin density is distributed over the entire molecule (Scheme 52). The extraordinary stability of aminoxyl radicals also results from this effect illustrated by the resonance structures of TEMPO (**221** and **221a**).



Scheme 52 Contributing structures of the GOMBERG radical (**197**) and TEMPO (**221**).

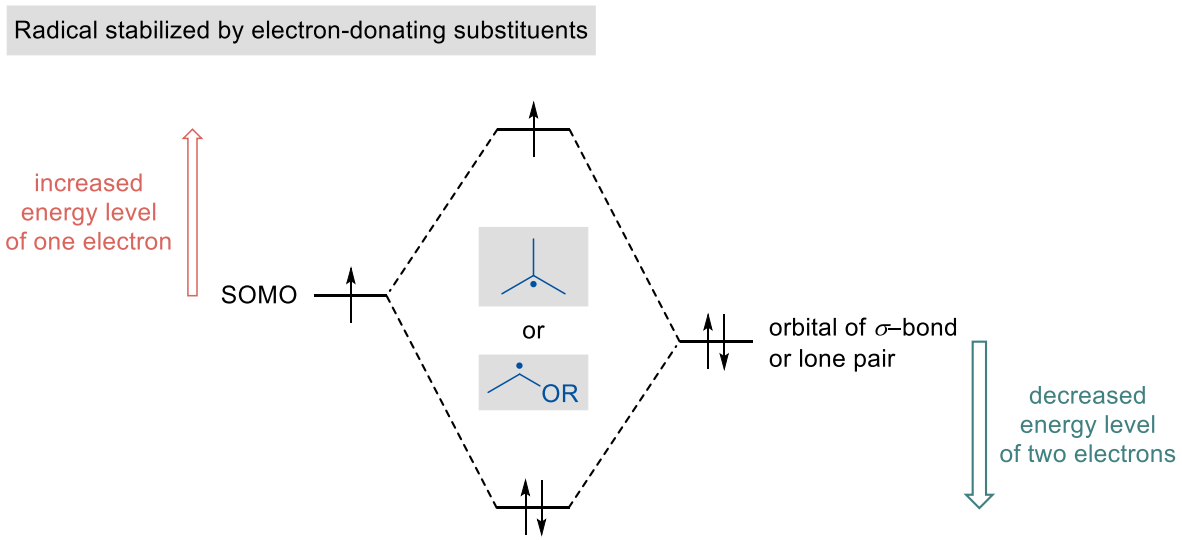
Moreover, radicals can be stabilized by conjugation with adjacent functional groups. Interestingly, it does not depend on whether the functional group is electron-withdrawing or electron-donating. For radicals that contain an electron-withdrawing carbonyl moiety in the α-position, the singly occupied *p* orbital can interact with the antibonding π^* orbital of the C=O double bond. The combination leads to two new molecular orbitals occupied by only one electron. The spin energy level of the unpaired electron is therefore lower, which stabilizes the radical (Scheme 53).[133]



Scheme 53 Stabilizing effect due to the interaction of the SOMO with an electron-withdrawing substituent.[133]

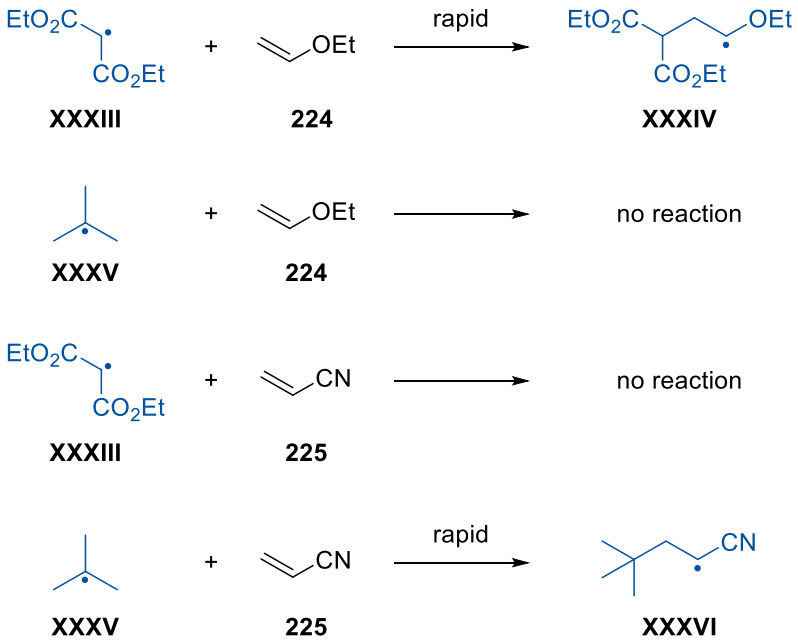
For radicals with electron-donating substituents, an overlap of the singly occupied molecular orbital (SOMO) with an orbital of a neighboring σ bond or a lone-pair occurs. This interaction generates two new orbitals occupied by three electrons. Because two experience a reduction in their energy lever, whereas only one SOMO electron is increased in its energy, stabilization follows here as well

(Scheme 54).[133] In the case of alkyl substituents, this effect is referred as hyperconjugation and explains why tertiary radicals are inherently more persistent than secondary and primary ones.[136]



Scheme 54 Stabilizing effect due to the interaction of the SOMO with an electron-donating substituent.[133]

The decrease or increase in the spin energy level of the unpaired electron also affects the reactivity of the radical (Scheme 55). The addition to the electron-rich vinyl ether **224** by the electrophilic malonyl radical **XXXIII**, which has a rather low spin energy level, occurs rapidly, while the *tert*-butyl radical (**XXXV**) does not form the desired adduct. On the other hand, the elevated energy level of the unpaired electron of the nucleophilic *tert*-butyl radical (**XXXV**) leads to a higher reactivity towards the electron-deficient acrylonitrile (**225**) while the malonyl radical **XXXVI** does not add to the olefin **233**.[135]

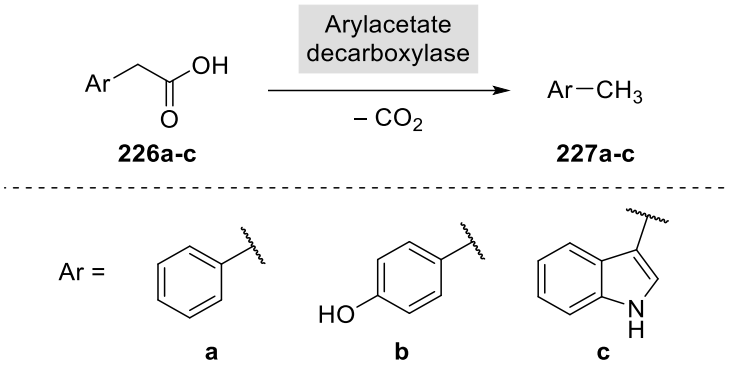


Scheme 55 Reactivity of nucleophilic and electrophilic radicals with electron-rich and electron-deficient olefins.[135]

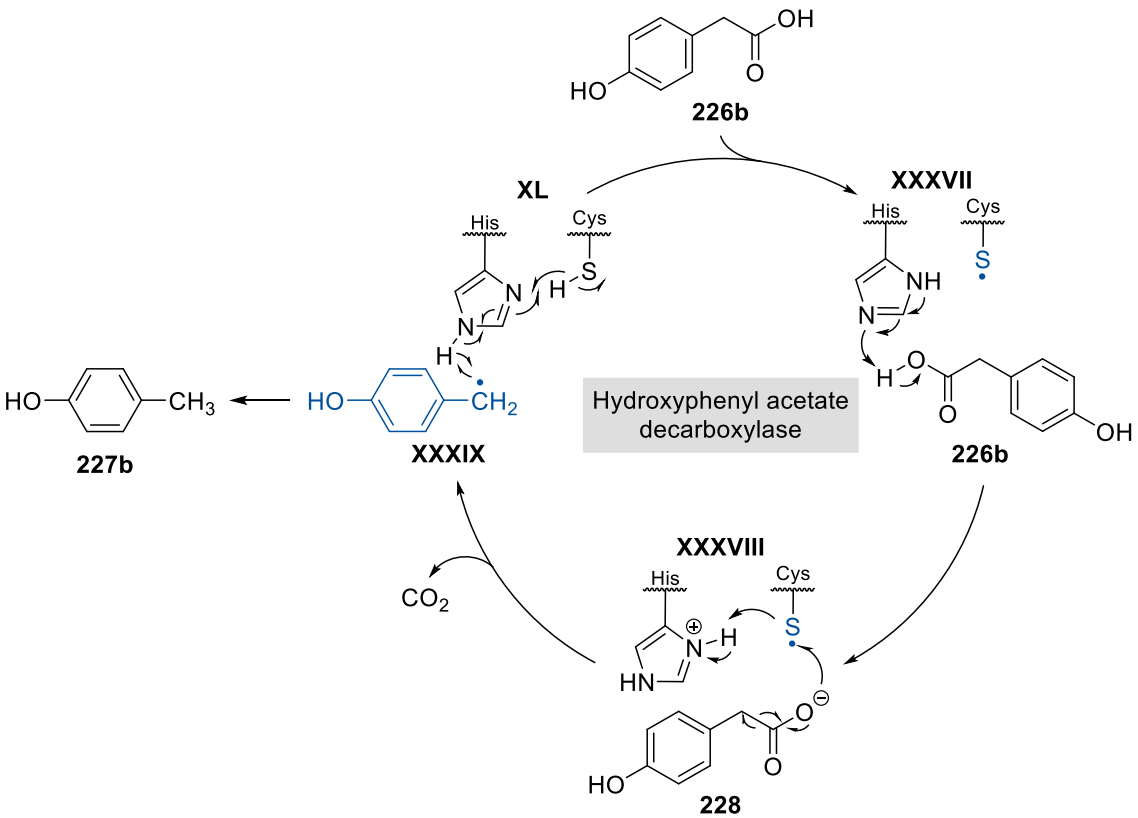
B1.4 Oxidative Radical Decarboxylations

Oxidative radical decarboxylations have been part of the synthetic chemist's toolbox since the development of the KOLBE electrolysis 175 years ago. Particularly within the last 10 years, a large number of methodologies based on radical decarboxylations have been developed due to the emerging prominence of photoredox catalysis and electrochemistry.

Oxidative radical decarboxylations have also been observed in biological processes. Thus, glycyl radical enzymes that decarboxylate arylacetates have been found in various bacterial species. To date, hydroxyphenyl acetate decarboxylase (HPAD), phenyl acetate decarboxylase (PAD) and indole acetate decarboxylase (IAD) have been identified which catalyze the conversion of phenylacetic acid (**226a**), *p*-hydroxyphenylacetic acid (**226b**) and 3-indoleacetic acid (**226c**) into toluene (**227a**), *p*-cresol (**227b**) and skatole (**227c**), respectively (Scheme 56).[137]



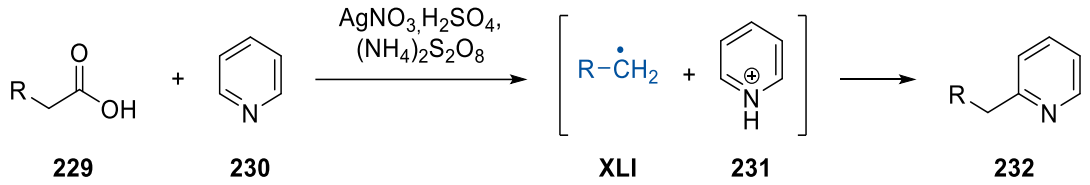
Scheme 56 General reaction scheme for radical decarboxylations catalyzed by arylacetate decarboxylases.[137]



Scheme 57 Proposed mechanism of the hydroxyphenyl acetate decarboxylase-mediated decarboxylation of *p*-hydroxyphenylacetic acid (**226b**).[138]

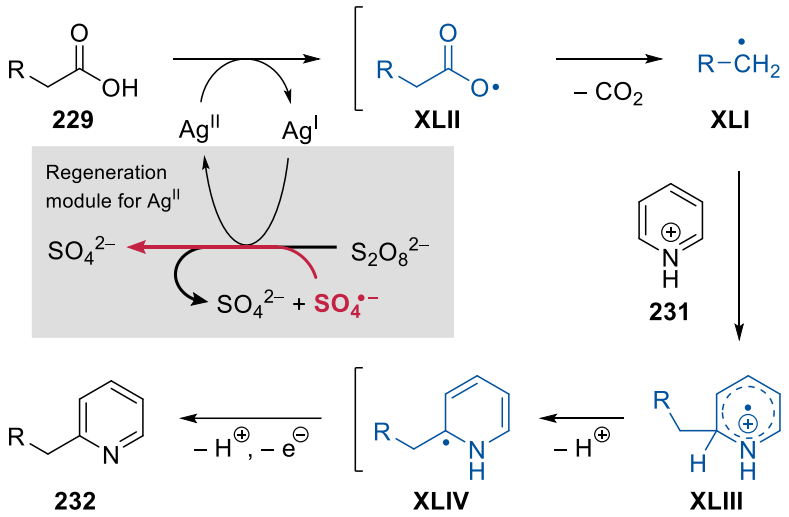
To date, the mechanistic details of arylacetyl decarboxylases have not been fully elucidated. However, they are thought to follow different pathways. The proposed mechanism of decarboxylation by HPAP is illustrated in Scheme 57. First, the carboxylic acid **226b** is deprotonated in the active pocket. Subsequent single-electron transfer from carboxylate **228** to thiyl radical **XXXVII** initiates decarboxylation. The resulting alkyl radical **XXXIX** then leads to the regeneration of the active pocket by the abstraction of a hydrogen radical.[138]

One of the most prominent name reactions in radical chemistry relies on a similar mechanism. In 1971, MINISCI reported on a radical substitution on electron-deficient heteroaromatic compounds **230** based on an oxidative decarboxylation of carboxylic acids **229** (Scheme 58).[139]



Scheme 58 MINISCI reaction based on oxidative decarboxylation.[139]

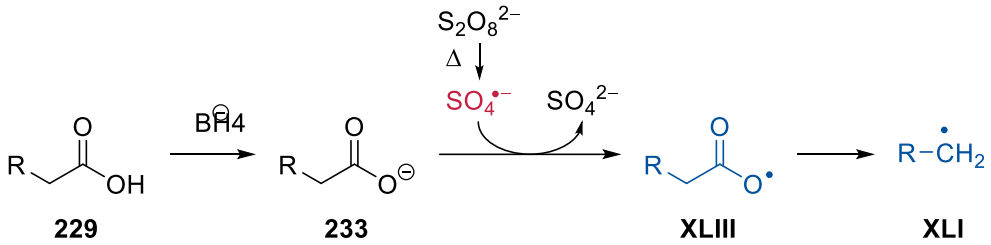
The original procedure incorporated silver(I) nitrate as a precursor for the generation of a highly reactive Ag(II) species using ammonium peroxydisulfate as oxidant. This process produces a sulfate anion and a sulfate radical. The active Ag(II) species is able to abstract a hydrogen atom from carboxylic acid **237**, initiating decarboxylation to yield radical **XLI**. Addition to pyridinium **231** gives radical cation **XLIII**, which then rearomatizes by deprotonation and oxidation to give alkylated pyridine **232**. In this step, a Ag(II) species or a sulfate radical acts as oxidant resulting in the formation of a Ag(I) species or a sulfate anion, respectively.[140,141]



Scheme 59 Proposed mechanism of the classical MINISCI protocol for the generation of alkyl radicals from alkyl carboxylic acids using silver(II).[140,141]

Still to this today, the method represents an important tool for the synthesis of functionalized heterocycles based on inexpensive and ubiquitously available carboxylic acids.[140] In addition, decarboxylative MINISCI-type alkyl radical formation processes have been widely used for C–C[142] and C–S[143] coupling reactions, ring closing cascades,[144–146] radical substitutions[147] and (pseudo)halogenations.[148][149]

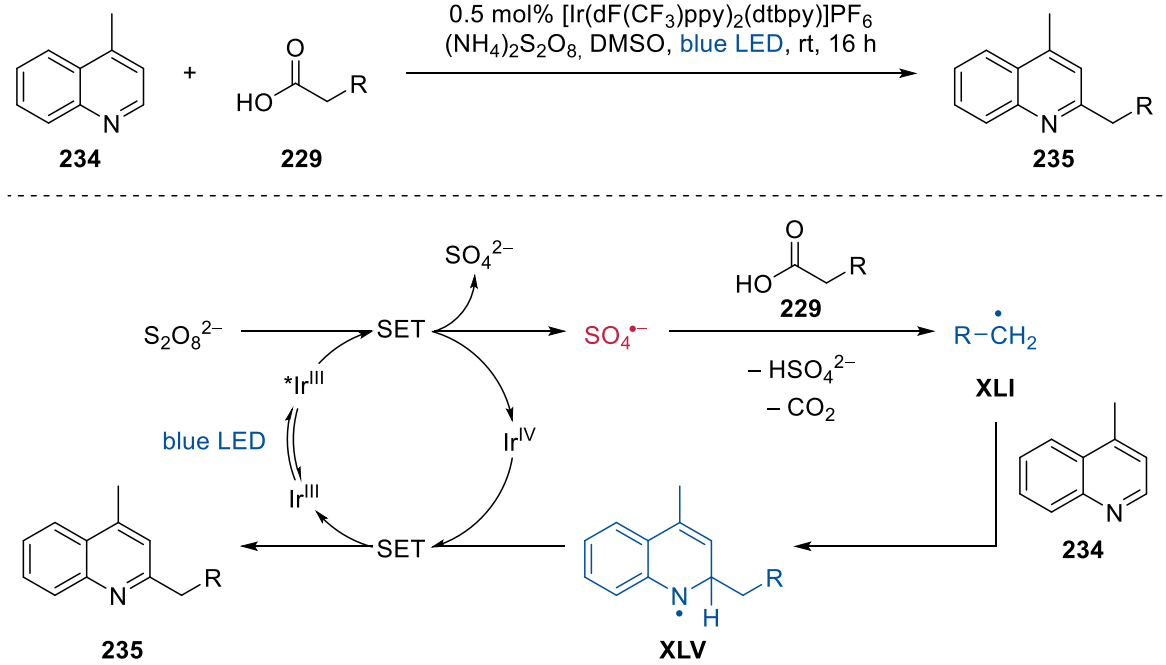
Despite the wide range of applications, some disadvantages persist. Usually, up to stoichiometric amounts of the expensive and toxic silver(I) salts are required.[143,144,150] However, in a few cases, it has been shown that the addition of a base can eliminate the need for transition-metal catalysis.[146,151,152] The sulfate radical, with a redox potential of 2.5-3.1 V, is a strong single-electron oxidant and therefore capable of oxidizing carboxylates formed *in situ* to generate carboxyl radicals (Scheme 60).[153]



Scheme 60 Generation of alkyl radicals by transition-metal free peroxydisulfate-mediated radical decarboxylation.[151]

Unfortunately, in the metal-free variants, but also in the classical silver-catalyzed processes, low selectivity is reflected in the fact that the carboxylic acid usually had to be used in excess. In addition, the strongly oxidizing conditions limit the substrate and reagent scope considerably.[141]

Modern approaches to perform oxidative radical decarboxylation in a more controlled manner under milder conditions are often based on photoredox catalysis.[140] The majority of these involve single-electron oxidation of carboxylates. In contrast, GLORIUS and co-workers reported in 2017 on a MINISCI-like alkylation reaction using an iridium-based photoredox catalyst relying on a hydrogen atom transfer (Scheme 61).[154] Their mechanistic investigations revealed that the excited catalyst initiates a radical chain process by reduction of a persulfate anion. The generated radical anion is able to abstract a hydrogen atom from carboxylic acid **229** leading to alkyl radical **XLI** by decarboxylation. Similar to the classical MINISCI reaction, this adds to the heterocycle **242**. Finally, rearomatization by oxidation through the photoredox catalyst provides product **235** and regenerates the catalyst.



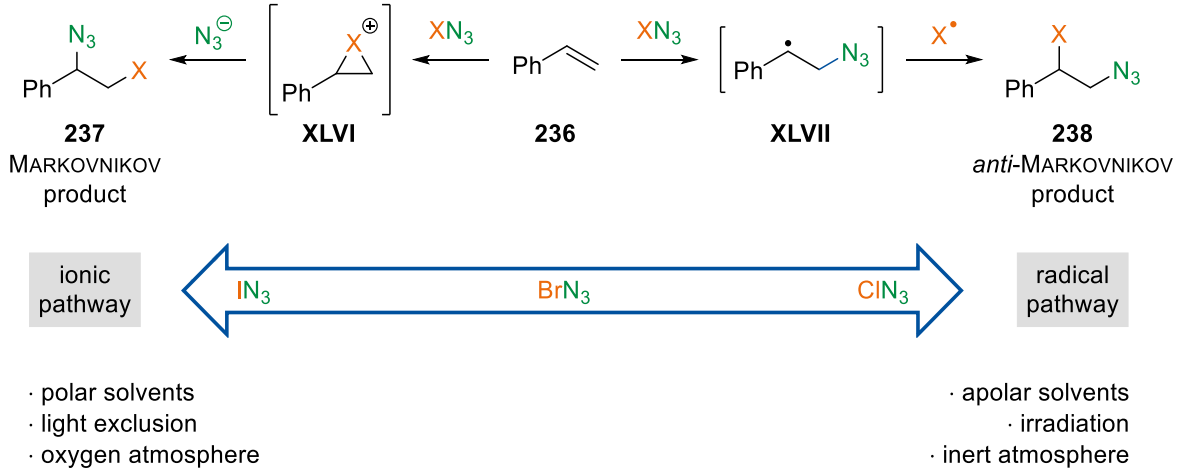
Scheme 61 Decarboxylative MINISCI-type decarboxylation using photoredox catalysis.[154]

B1.5 Halogen Azides in Organic Chemistry

Within the family of interhalogens, the halogen azides are an extremely fascinating but also preparatively difficult class of compounds, whose handling requires a considerable degree of dexterity due to their extraordinary reactivity, volatility and potential toxicity. Iodine azide (IN_3) was first synthesized in 1900 by HANTZSCH,[155] followed by chlorine azide (ClN_3) in 1908 by RASCHIG,[156] bromine azide (BrN_3) in 1925 by SPENCER[157] and fluorine azide (FN_3) in 1942 by HALLER.[158] All of them were reported to be capable of violent explosions, with stability appearing to increase slightly in the order $FN_3 < IN_3 < BrN_3 < ClN_3$. In addition, BrN_3 was reported to be sensitive to hydrolysis leading to decomposition into its elements, which further complicates handling.[159]

Nevertheless, halogen azides have attracted attention of synthetic organic chemists. The 1,2-addition of ClN_3, BrN_3 or IN_3 to olefins, extensively studied by HASSNER and BOERWINKLE beginning in the 1960s, provides access to synthetically valuable functionalized products.[160,161] Azides are suitable as 1,3-dipoles for [3+2] cycloadditions or can be readily reduced to the corresponding amines.[162] The halogen can either be substituted by S_N reactions, e.g., by attack of the amine to form aziridines, serve as a starting material for cross-coupling reactions or can be eliminated to form vinyl azides.[163,164]

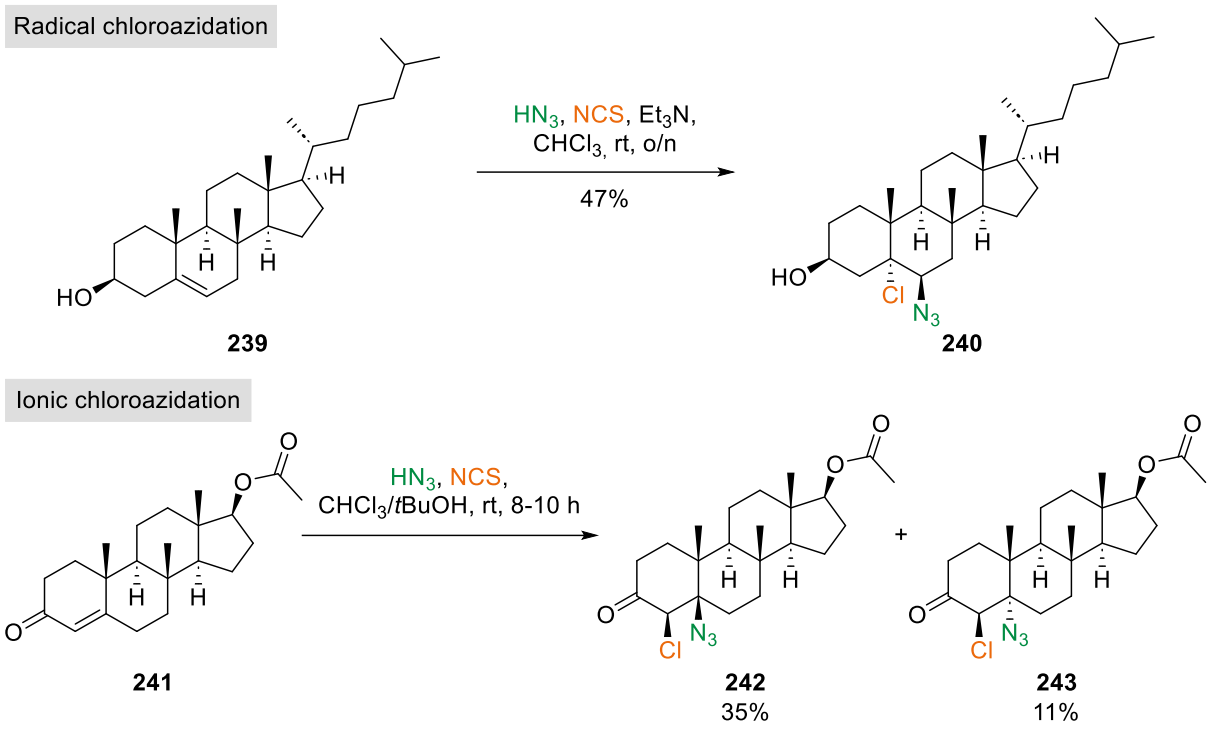
Interestingly, the addition to olefins can proceed via an ionic or a radical pathway, resulting in products with contrary regioselectivity. According to the electronegativity trend $I < N_3 = Br < Cl$, the ionic addition of IN_3 is strongly preferred, while the *anti*-MARKOVNIKOV products resulting from a radical pathway are obtained in the majority of 1,2-functionalization with ClN_3. However, by adjusting the conditions, the opposite regioselectivity can be obtained. Polar solvents, light exclusion and an oxygen atmosphere trigger an ionic pathway, while the use of solvents with low polarity, irradiation with light and an inert atmosphere initiate a radical chain process (Scheme 62).[161]



Scheme 62 Reaction pathway tendency of halogen azides and conditions triggering the ionic or radical pathway.[161]

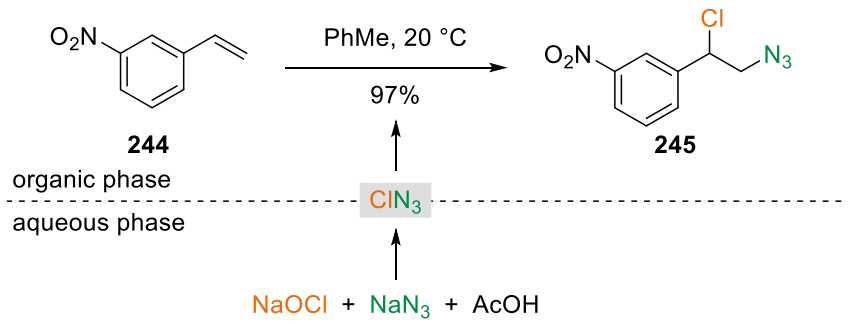
Due to the significant hazards associated with the preparation of halogen azides, attention has been given to the development of methods to generate these species *in situ* under controlled conditions.

For chlorine azide, a combination of *N*-chlorosuccinimide (NCS) and the highly toxic hydrazoic acid has proven successful for this purpose (Scheme 63). Applying chloroform as solvent, the *anti*-MARKOVNIKOV product was formed, while the addition of *tert*-butanol as a co-solvent led to the MARKOVNIKOV products by an ionic mechanism.[165,166]



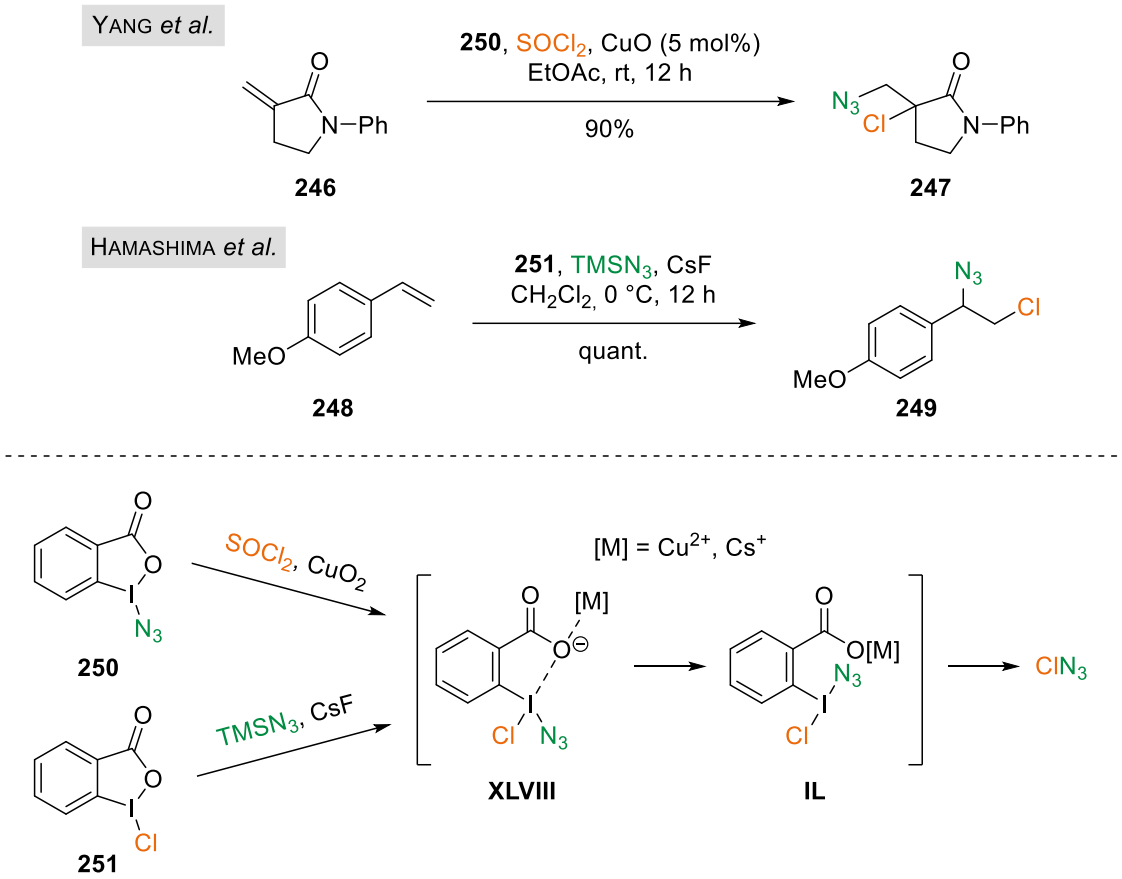
Scheme 63 Radical and ionic chloroazidation of steroids by EICHHORN *et al.*[165,166]

In 2015, FINN and co-workers reported a two-phase approach for the 1,2-addition of chlorine azide to structurally versatile olefins (Scheme 64). The interhalogen species was first generated in the aqueous phase by the reaction of sodium azide, sodium hypochlorite and acetic acid before moving into the organic layer. The subsequent addition gave for the majority of cases the products expected from a radical pathway.[167]



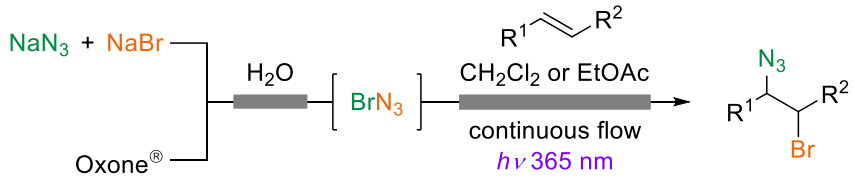
Scheme 64 1,2-Chloroazidation of alkenes by a two-phase approach.[167]

The most recently developed methodologies on chloroazidations are based on benziodoxolone-type reagents (Scheme 65). In 2016, YANG *et al.* reported on a radical addition of chlorine azide to olefins. The reactive species was generated from the Zhdankin's reagent (**250**), thionyl chloride and copper(II) oxide.[168] In the same year, 1-chloro-1,2-benziodoxol-3(1*H*)-one (**251**), trimethylsilyl azide and cesium fluoride were identified as suitable reagents for an ionic counterpart by HAMASHIMA and co-workers.[169] In both cases, the iodine(III) reagent is activated by the metal cation leading to the formation of a iodosochloride-azide species **IL** which generates chlorine azide by reductive elimination.



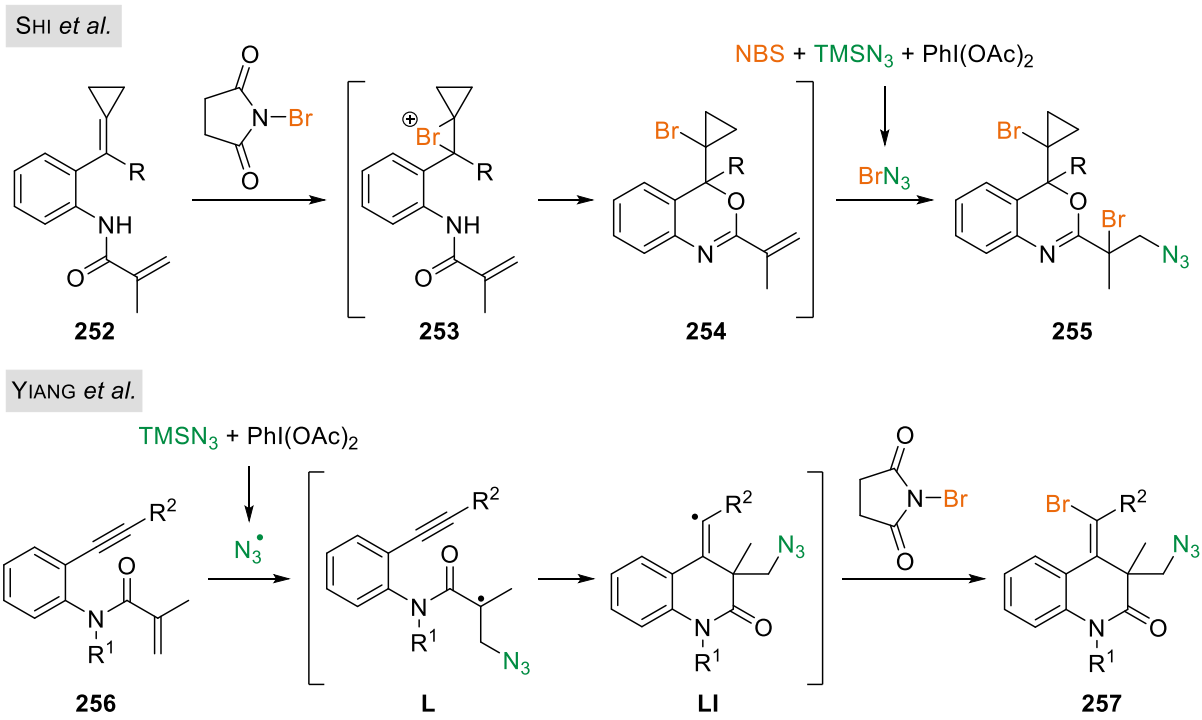
Scheme 65 Chloroazidation of olefins based on benziodoxolones **250** or **251**.[169]

The chemistry of bromine azide was still much less processed. For the radical bromoazidation of olefins using BrN_3 prepared *in situ*, only one method has been described in literature. In 2016, KAPPE and co-workers reported on a continuous flow set-up allowing the generation of the interhalogen species from aqueous solutions of sodium bromine, sodium azide and Oxone® and the direct addition to olefins in organic solvents under irradiation with UV light. The yields obtained were good to excellent, but only styrene-type substrates have been applied.[163]



Scheme 66 Radical bromoazidations of olefins in flow by KAPPE *et al.*[163,170]

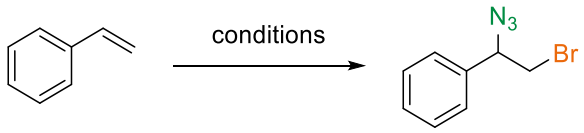
Furthermore, the literature provides examples of ring closing cascades initiated by mixtures of *N*-bromosuccinimide (NBS), trimethylsilyl azide and (diacetoxyiodo)benzene. However, the proposed mechanisms for these conversions vary substantially. According to SHI *et al.*, compound **252** is first ionically bromocyclized by NBS, resulting in alkene **254**, which subsequently undergoes radical 1,2-functionalization by bromine azide formed *in situ*.[171] In contrast, YIANG *et al.* assume that the cyclization of alkyne **256** is initiated by azide radicals, formed from trimethylsilyl azide and (diacetoxyiodo)benzene. According to this proposal, NBS is attacked by an alkyl radical at the end of the cascade, leading to the desired product **257**.[172]



Scheme 67 Proposed mechanisms for cyclizations initiated by mixtures of NBS, $TMSN_3$ and $PhI(OAc)_2$.[171,172]

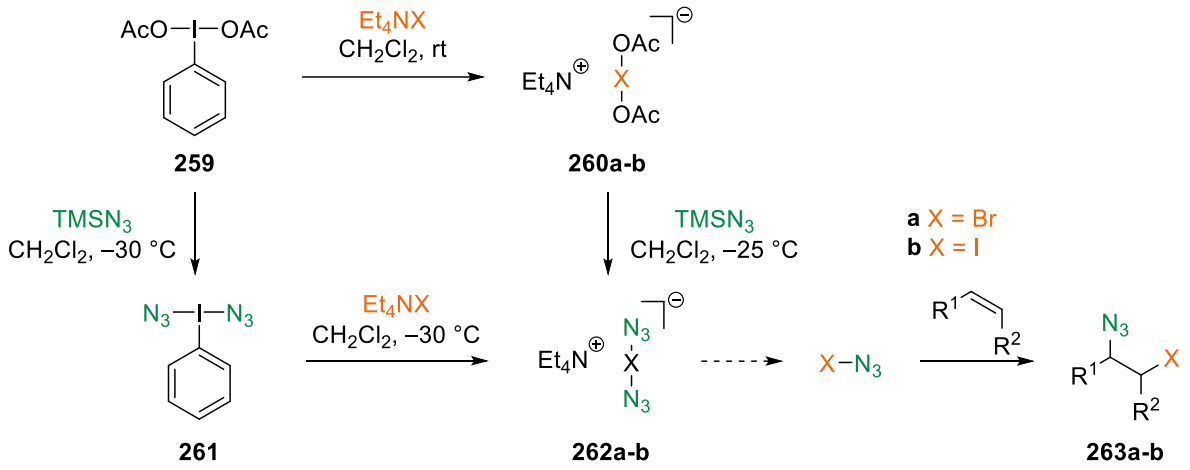
Ionic bromoazidations were described under similar conditions. The reagents used here were trimethylsilyl azide either in combination with NBS and an oxidative catalyst (metal triflate or iodine) or with *N*,*N*-dibromo-*p*-toluenesulfonamide (Table 15).[173–175]

Table 15 Literature-known conditions for the ionic bromoazidation of olefins.



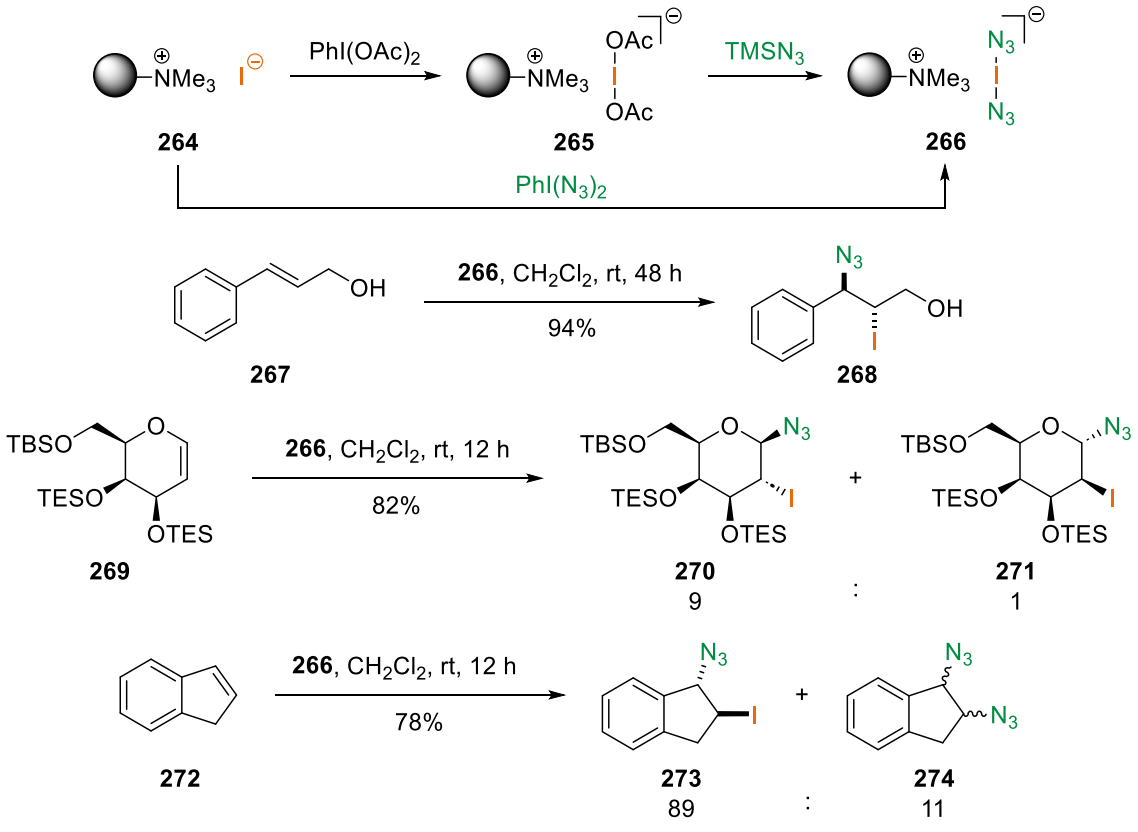
Entry	Conditions	Yield / %
1[173]	$Zn(OTf)_2$ (5 mol%), NBS, $TMSN_3$, CH_2Cl_2, 0 °C, 10 min	85
2[174]	$TsNBr_2$, $TMSN_3$, MeCN, rt, 10 min	82
3[175]	I_2 (10 mol%), NBS, $TMSN_3$, CH_2Cl_2, rt, 1 h	79

In 1999, KIRSCHNING and co-workers reported on a highly innovative method for ionic bromo- and iodoazidations based on bis(azido)bromate(I) and bis(azido)iodate(I) complexes (Scheme 68). These halonium reagents were obtained by the oxidation of tetraethylammonium bromide or iodide with the highly explosive (diazidoiodo)benzene (**261**), which was formed *in situ* from (diacetoxyiodo)benzene (**259**) and trimethylsilyl azide. A less hazardous procedure was to first form bis(acetoxy)haloate(I) **260** from the halide salt and (diacetoxyiodo)benzene (**259**) followed by ligand exchange to yield the bis(azido) species **262**. It is assumed that the halonium reagents **262a** and **262b** slowly release the corresponding interhalogen species, which are capable of 1,2-functionalizing alkenes in a highly *anti*-selective manner via an ionic pathway.[176]



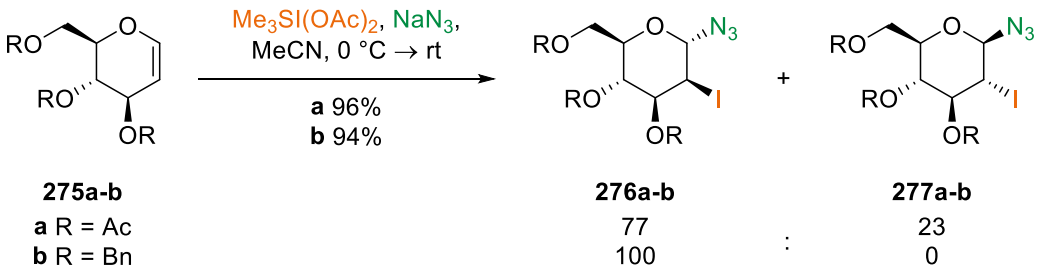
Scheme 68 Preparation of bis(azido)haloate(I) complexes **262a-b**.[176]

In the same year, a polymer-bound variant of the bis(azido)iodate(I) complex was also reported by the KIRSCHNING group (Scheme 69). By utilizing Amberlyst® A26 in its iodide form (**264**), non-explosive orange-colored ion-exchange resin **266** was obtained which can be stored for several months in the dark under argon atmosphere at −15 °C without loss of activity. The reagent was successfully applied for the iodoazidation with a variety of alkenes resulting in good to excellent yields and diastereoselectivities. Interestingly, the reaction with indene (**272**) afforded the 1,2-diazo compound **274** as a side product. However, the relative stereochemistry of this compound was not given in the publication and it was not discussed whether it was formed from **273** by an S_N reaction of an azide anion or directly from indene (**272**) by radical diazidation.[177]



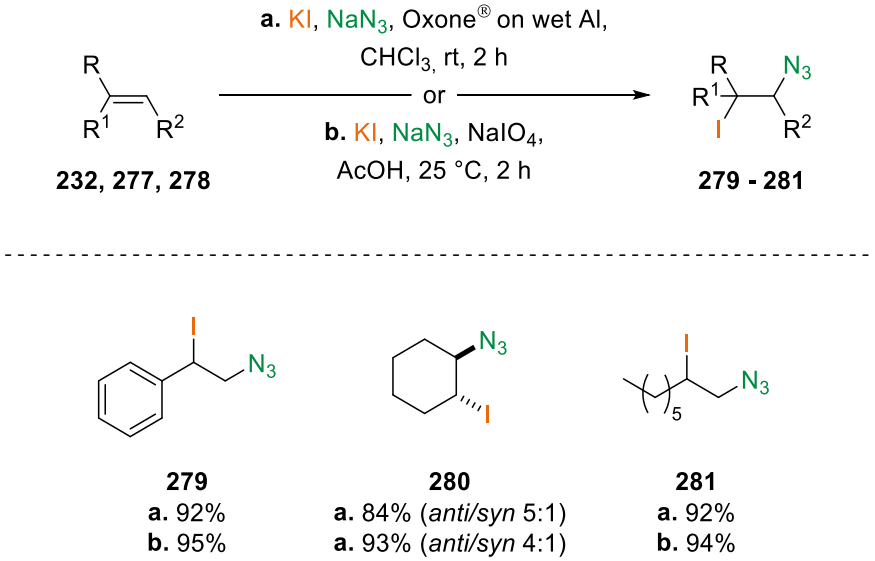
Scheme 69 Iodoazidation of various alkenes using polymer-bound bis(azido)iodate(I) **266** prepared from Amberlyst® A26 in its iodide form (**264**).[177]

In 2016, this approach was adopted by KASHYAP and his colleagues. Utilizing trimethylsulfonium as counter cation, the authors were able to isolate the bis(acetoxy)iodate(I) complex as a pure salt. By treating this halonium species with trimethylsilyl azide or sodium azide in acetonitrile, the corresponding bis(azido)iodate(I) complex could be formed *in situ*. With this species, a number of glycals could be 1,2-functionalized in excellent yields but with varying diastereoselectivity (Scheme 70).[178]



Scheme 70 Ionic iodoazidation of glycals using *in situ* formed $Me_3SI(N_3)_2$.[178]

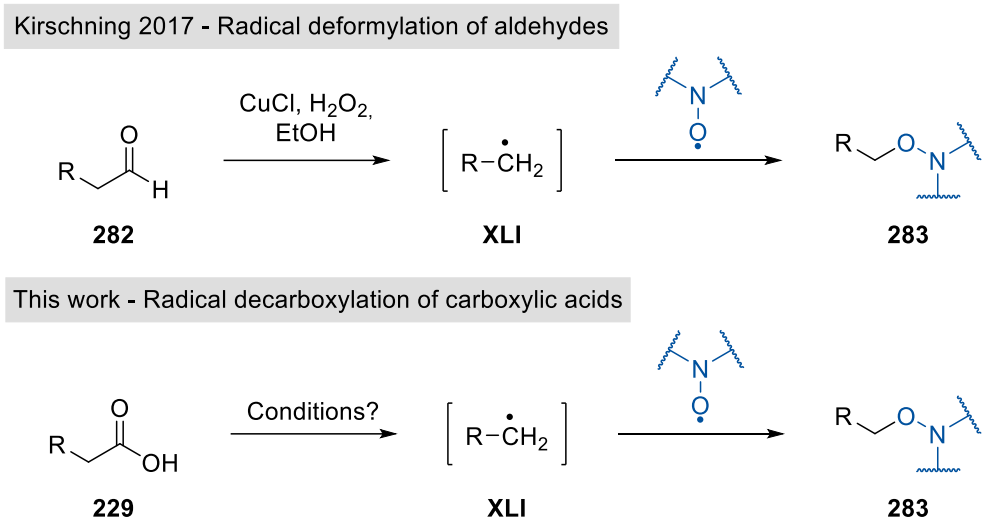
For radical iodoazidations, the generation of iodine azide by treating solutions of iodide and azide salts with an oxidizing reagent has proven effective. In 2001, MARCOTULLIO *et al.* reported on an efficient method for *anti*-MARKOVNIKOV addition of iodine azide formed from potassium iodide, sodium azide and Oxone® supported on wet alumina in chloroform.[179] A comparable approach was taken by SUDALAI *et al.* in 2010, who used sodium periodate as the oxidant and acetic acid as solvent. Both procedures gave comparable yields and diastereoselectivities (Scheme 71).



Scheme 71 Radical iodoazidations of alkenes by MARCOTULLIO *et al.*[179] and SUDALAI *et al.*[180]

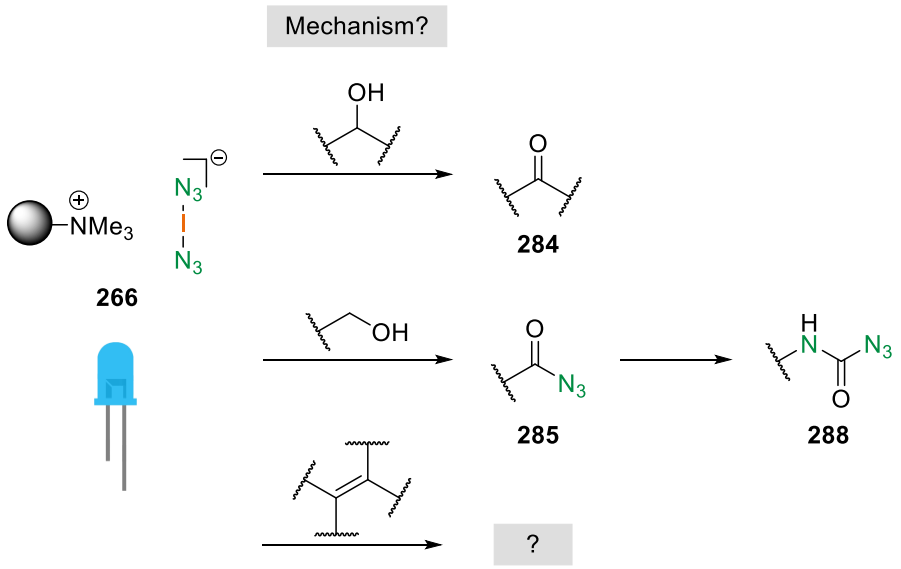
B2 Project Aim

Inspired by the work on the synthesis of alkoxyamines by radical deformylation of aldehydes,[181,182] a MINISCI-type decarboxylation was to be developed in which the alkyl radical formed is trapped by an aminoxyl radical (Scheme 72). The difficulty encountered was the need to control the selectivity of the strong oxidation reagents required. The synthetic relevance of the novel methodology was to be demonstrated by its utilization in the multistep synthesis of a bioactive compound.



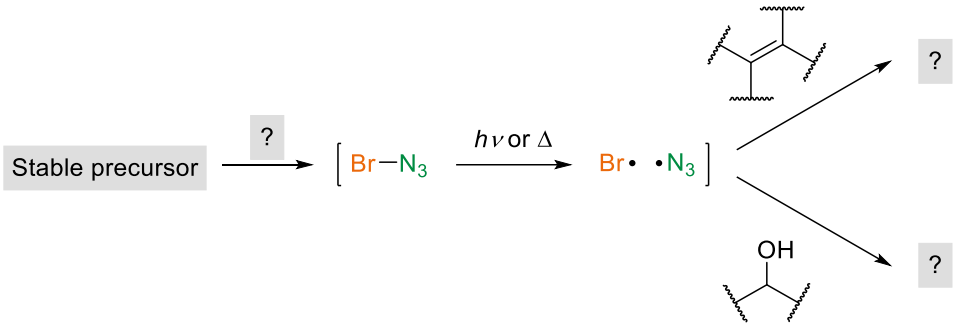
Scheme 72 Development of a radical decarboxylative aminoxylation of free carboxylic acids.

A further subproject was based on the work of KÖSEL. In her master's thesis, she demonstrated the ability of iodine azide released from ion exchange resin **266** to selectively oxidize secondary alcohols to the corresponding ketones **284** under photochemical conditions. Primary alcohols reacted only sluggishly to yield the acyl azides **285**, which underwent CURTIS rearrangement and a second azidation giving rise to the corresponding carbamoylazides **286**.[183] The aim of this project, in addition to elucidating the mechanistic details of these transformations, was to develop broader applications of polymer-bound iodine azide under irradiation with blue LED light.



Scheme 73 Photochemical transformations with iodine azide after release from ion-exchange resin **266**.

Lastly, the newly gained knowledge about the reactivity of iodine azide should be harnessed to advance the radical chemistry of bromine azide. Since this compound is extremely unstable and explosive, methods were to be developed to generate bromine azide *in situ* under controlled conditions. Subsequently, it should be validated whether the transformations that are feasible with iodine azide also yield corresponding products in transformations with bromine azide.

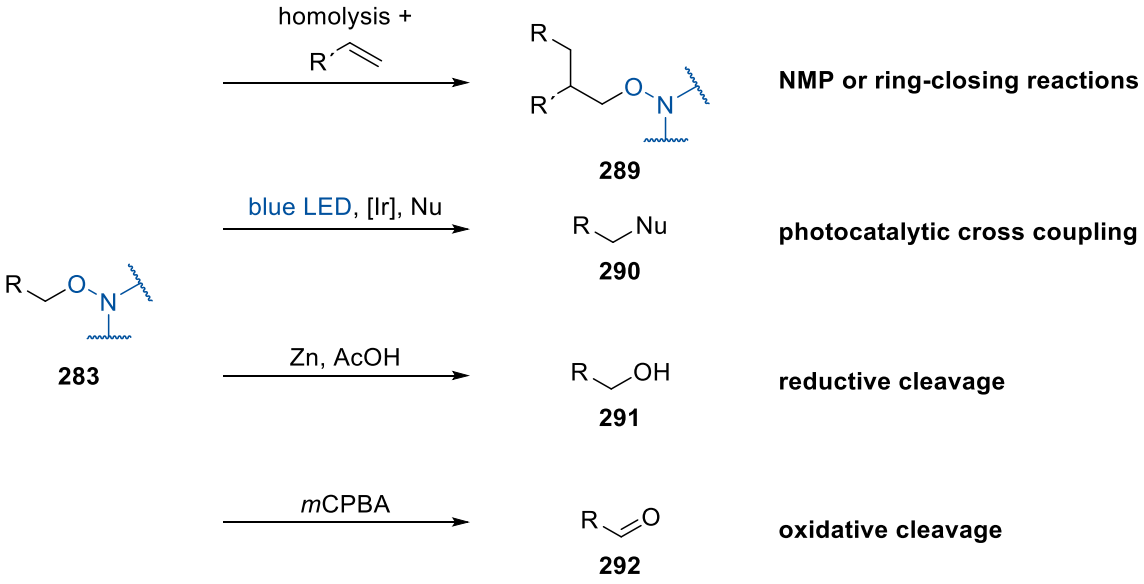


Scheme 74 Exploration of the chemistry of bromine azide under photochemical and thermal conditions.

B3 Results and Discussion

B3.1 Transition-Metal Free Decarboxylative Aminoxylation of Carboxylic Acids

TEMPO (**221**), the most prominent and widely used aminoxyl radical, is particularly applied in method development for mechanistic studies. It is able to capture highly reactive radical intermediates and thus suppressing the formation of products resulting from radical chain processes. The reaction of TEMPO (**221**) or other aminoxyl radicals with alkyl radicals produces alkoxyamines, which have found application as important group of reagents and functional groups in various fields of organic chemistry (Scheme 75). As described in Section B1.1 (Scheme 46b), this species can be homolytically cleaved under thermolytic conditions, which gives rise to a highly reactive alkyl radical and the persistent aminoxyl radical. In combination with alkenes a migratory insertion into the double bond is observed.[130] This unique reactivity is the basis for the application as initiators for nitroxide-mediated polymerization (NMP) as well as for ring-closing reactions in synthetic organic chemistry.[129,184] Furthermore, KNOWLES *et al.* reported on the mesolytic cleavage of alkoxyamines by photoredox catalysis. Cross-coupling of the resulting carbocations with various nucleophiles led to the formation of C-C, C-N or C-O bonds.[185] Beyond these applications, alkoxyamines can be readily converted into alcohols[186] or carbonyl compounds.[141,187]



Scheme 75 Selected applications of alkoxyamines in organic chemistry.[141]

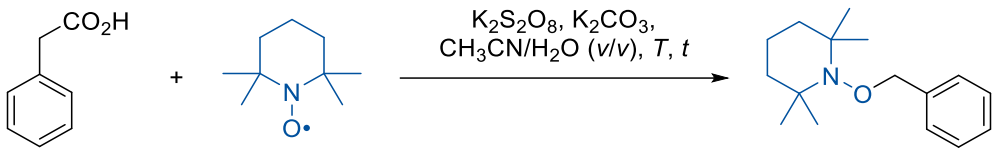
Previous methods for the formation of alkoxyamines started from haloalkanes,[188,189] boronates,[190] boranes,[191] aldehydes[181,182] or redox-active esters.[192] In the context of MINISCI-type reactions, TEMPO (**221**) has frequently been used to confirm the radical mechanism. However, in the majority of cases, the formation of alkoxyamines was not proven[151] or only by GC/MS or LC/MS analysis.[193] In the only two cases described in the literature where the resulting alkoxyamines were isolated, the experimental procedures are not clear[194] or even not reported.[195] In both cases, overstoichiometric amounts of the carboxylic acid were applied, and it was not specified to which starting material the reported yields referred. The challenge of this transformation arises from the fact that oxidative decarboxylations, as described in Section B1.4, are generally characterized by low chemoselectivity.

Furthermore TEMPO (**221**) and related aminoxyl radicals can be oxidized by silver(II) or persulfate salts.[196]

Therefore, a program to develop a method for the formation alkoxyamines by a radical decarboxylation of carboxylic acids was initiated utilizing phenylacetic acid (**226a**) as test substrate. Initially, the conditions reported by ZHOU *et al.* for a transition-metal-free oxidative decarboxylation with $K_2S_2O_8$ were applied. A solution of carboxylic acid **226a**, TEMPO (**221**) (2.00 eq.), potassium persulfate (1.50 eq.) and K_2CO_3 (0.75 eq.) in a 1:1 mixture of acetonitrile and water was stirred for 2 hours at room temperature (Table 16, Entry 1).[151] The formation of the product was observed by LC/MS analysis but only trace amounts of **226a** were visible in the crude ^{1}H NMR spectrum. Using twice the amount of oxidant and base at 60 °C, the product was formed in 6% yield (Entry 2). If the ratio of acetonitrile to water is set to 1:2, the yield increased to 41% (Entry 3). The reduction of the equivalents of base and/or oxidant resulted in a drop in yields (Entries 4 – 6). By lowering the temperature to room temperature and omitting acetonitrile, an optimized yield of 91% was achieved (Entries 7 – 9).

The optimized conditions are also the most convenient and "greenest", as only water was used as solvent and no additional transition-metal catalyst was necessary. This procedure represents one of the simplest methods for the preparation of alkoxyamine **293a,** which represents a useful initiator for the nitroxide-mediated polymerization.[188]

Table 16 Optimization of the transition-metal free decarboxylative aminoxylation of carboxylic acid **226a**; ^{1}H NMR yields using naphthalene as an internal standard; yields in brackets are isolated yields.



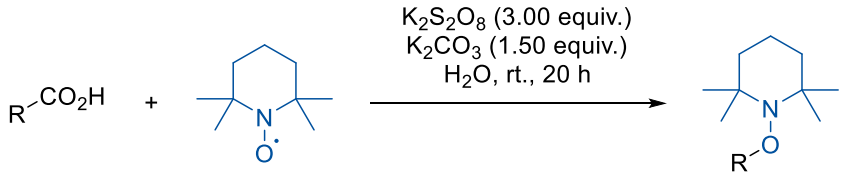
226a **221** 2.00 equiv. **293a**

Entry	$K_2S_2O_8$ / eq.	K_2CO_3 / eq.	MeCN:/H_2O (*v:v*)	*T* / °C	*t* / h	Yield / %
1	1.50	0.75	1:1	rt.	2	traces
2	3.00	1.50	1:1	60	2.5	6
3	3.00	1.50	1:2	60	2.5	41
4	3.00	0.75	1:2	60	20	traces
5	1.50	1.50	1:2	60	20	4
6	1.50	0.75	1:2	60	20	traces
7	3.00	1.50	1:3	60	20	65
8	3.00	1.50	0:1	40	20	86
9	3.00	1.50	0:1	rt	20	91 (85)

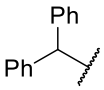
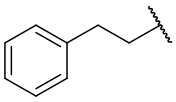
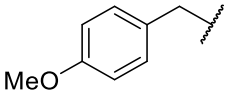
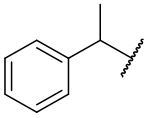
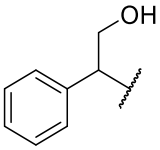
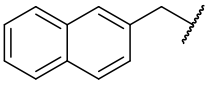
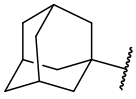
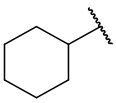
The optimized conditions were then applied to several other commercially available carboxylic acids **294b-i** to study the substrate scope of this transformation (Table 17). Unfortunately, only alkoxyamines **293c**, **293g** and **293i** could be generated in significant yields. In all the other cases, the

products only trace amounts of the products were observed by LC/MS analysis. In the cases of **294b** and **294d**, decarboxylation succeeded, but instead of the formation of the alkoxyamines **295b** and **295d**, the corresponding acetophenone respectively benzaldehyde analogues were isolated. Carboxylic acids **294e** and **294f** led to crude mixtures of several carbonyl compounds. For **294h** and **294i** the formation of TEMPO-adducts by non-decarboxylative C-H activations were observed.

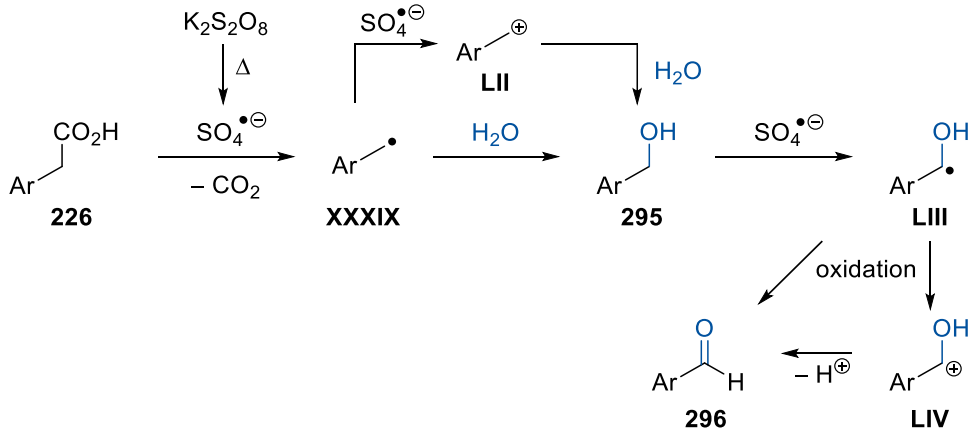
Table 17 Substrate scope of the transition-metal free decarboxylative aminoxylation of carboxylic acids **294b-i** in water; ^{1}H NMR yields using naphthalene as an internal standard; yields in brackets are isolated yields.



294b-i **221** 2.00 equiv. **293b-i**

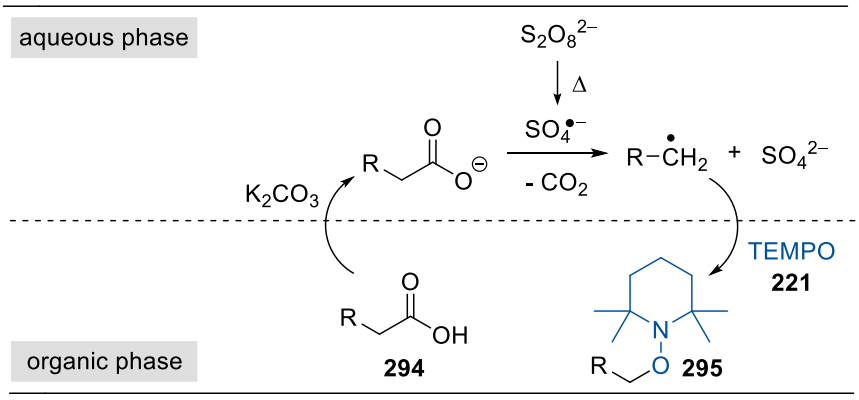
Entry	Substrate	Yield /%	Side products
1	 **294b**	traces	Ph_2CO (59%)
2	 **294c**	25	mixture of carbonyl compounds
3	 **294d**	traces	4-OMe-BzH (70%)
4	 **294e**	traces	mixture of carbonyl compounds
5	 **294f**	traces	mixture of carbonyl compounds
6	 **294g**	(72)	traces of naphthalene carbaldehyde
7	 **294h**	traces	TEMPO-adducts
8	 **294i**	17	TEMPO-adducts

A persulfate-mediated decarboxylative oxidation of arylacetic acids in water has already been described by BHAT *et al.* in 2017.[197] According to the proposed mechanism (Scheme 76), decarboxylation occurs first, after which the radical **XXXIX** is either directly captured by water or oxidized to the carbocation **LII** followed by nucleophilic attack of H_2O. The resulting alcohol **295** is then oxidized to the corresponding carbonyl compound **296**.[197] Since electron-donating substituents are able to stabilize the benzylic carbocation, it is likely that this led to favoring the overoxidation observed in the cases of **294b** and **294d**.



Scheme 76 Proposed mechanism for the persulfate-mediated decarboxylative synthesis of aldehydes and ketones.[197]

To suppress this side reaction, the use of a biphasic system was envisaged. It was assumed that this would lead to the oxidant being kept in a separate compartment from the aminoxyl and alkyl radicals. Mechanistically, carboxylic acid **294** should first be deprotonated at the phase boundary with potassium carbonate as the base. Since the carboxylate and the peroxodisulfate salt are water soluble, the oxidative decarboxylation should take place in the aqueous phase. The less polar alkyl radical formed should in turn be trapped in the organic phase by TEMPO (**221**) to give the alkoxyamine **295**.[141]

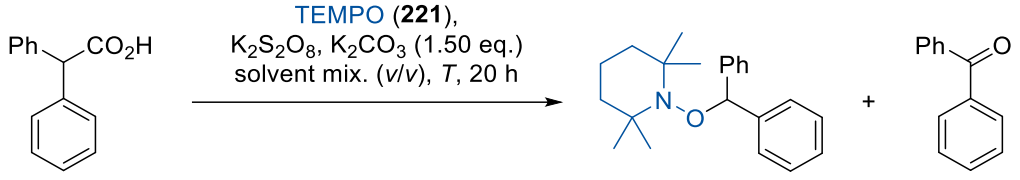


Scheme 77 Proposed phase-transfer concept for the decarboxylative aminoxylation in a biphasic solvent system.[141]

Based on this hypothesis, a new optimization series was carried out (Table 18). Starting point were the previously described conditions, except that a 1:1 mixture of 1,2-dichloroethane (DCE) and water was used as solvent (Entry 2). Under these conditions, a yield of 11% was achieved with carboxylic acid **294b**. By increasing the temperature and decreasing the amount of water, the yield of

alkoxyamine **293b** was improved, however, there was still a large amount of benzophenone **297** formed (Entry 3). By reducing the amount of oxidant, by-product formation was mostly suppressed. By reducing the amount of oxidant, by-product formation was largely suppressed, and further adjustment of the solvent ratio resulted in an optimized yield of 60% (Entry 5). The high effectiveness of the biphasic approach was also evidenced by the fact that the yield was similar when only one equivalent of TEMPO (**221**) was applied (Entry 6). The counterion of the oxidant exerts a non-negligible influence on the transformation, as shown by the decreased yields when sodium or ammonium persulfate was used (Entries 7 – 8). Lastly, the reaction was repeated using acetonitrile or DMF as co-solvents (Entries 9 – 10), resulting in lower yields and thus confirming the need for a biphasic system.

Table 18 Optimization of the transition-metal free decarboxylative aminoxylation of carboxylic acid **294b**; ^{1}H NMR yields using naphthalene as an internal standard; yields in brackets are isolated yields.



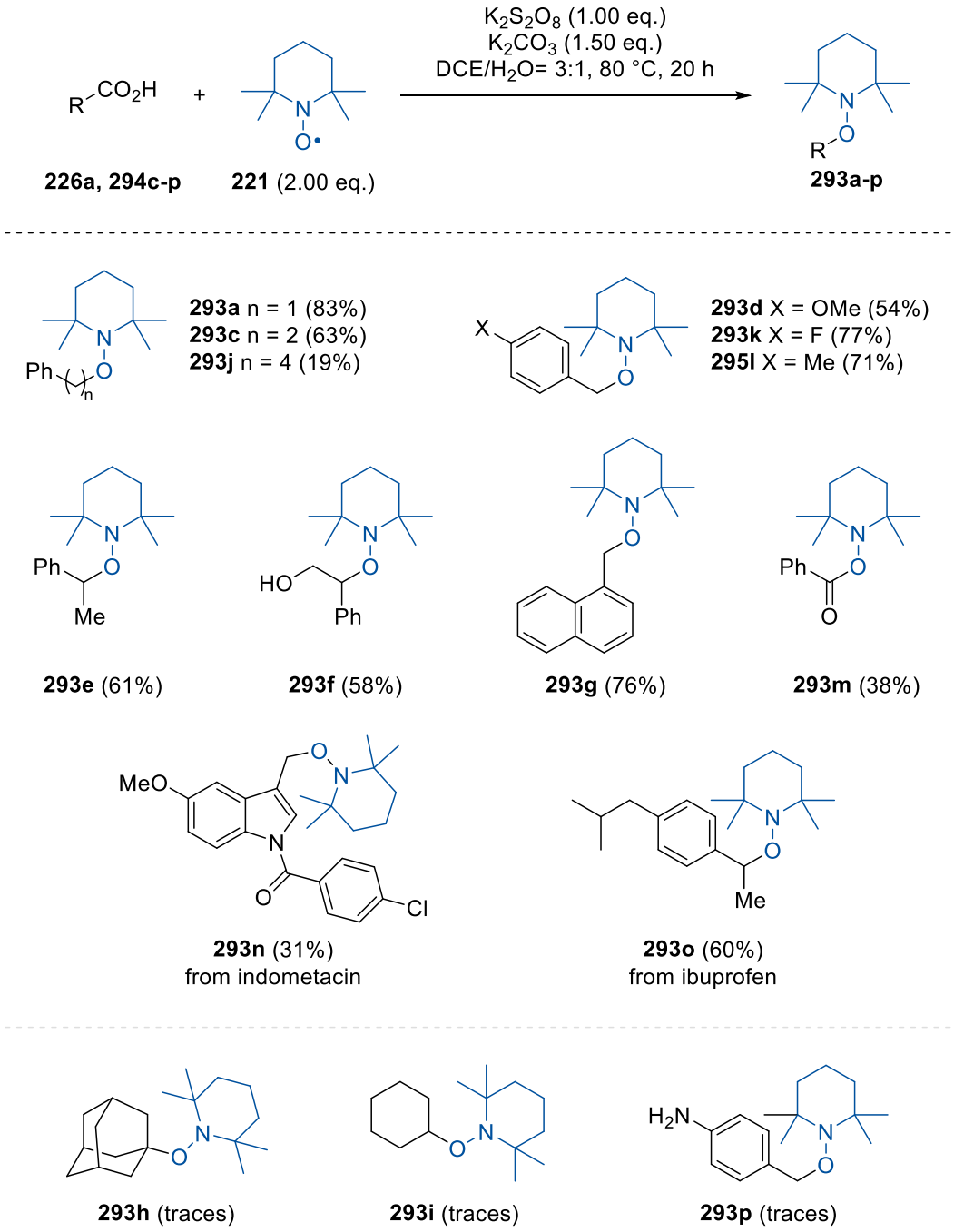
294b **293b** **297**

Entry	$K_2S_2O_8$ / eq.	TEMPO / eq.	Solvent mix. (*v:v*)	*T* / °C	293b / %	297 / %
1	3.00	2.00	H_2O	rt	traces	59
2	3.00	2.00	DCE/H_2O (1:1)	rt	11	39
3	3.00	2.00	DCE/H_2O (2:1)	80	28	30
4	1.00	2.00	DCE/H_2O (2:1)	80	49	13
5	1.00	2.00	DCE/H_2O (3:1)	80	60 (57)	11
6	1.00	1.00	DCE/H_2O (3:1)	80	(56)	n.d.
7[a]	1.00	2.00	DCE/H_2O (3:1)	80	46	22
8[b]	1.00	2.00	DCE/H_2O (3:1)	80	27	28
9	1.00	2.00	MeCN/H_2O (3:1)	80	2	36
10	1.00	2.00	DMF/H_2O (3:1)	80	3	2

[a] $Na_2S_2O_8$ was used instead of $K_2S_2O_8$ [b] $(NH_4)_2S_2O_8$ was used instead of $K_2S_2O_8$

With the optimized conditions in hand, the scope and limitations of the transformation were investigated (Scheme 78). The main focus was on arylacetic acid derivatives, which gave medium to high yields due to the intermediate formation of an aryl-stabilized benzyl radical. In contrast, reduced yields were obtained when arylpropionic acid **294c** and aryl valeric acid **294j** were employed. Likewise, benzyl cation-stabilizing substituents such as the 4-methoxy group of **294d**, which favor overoxidation to the corresponding acetophenone derivative, had a negative effect on yield. The use of the toluene derivative **294l** and tropic acid **294f** demonstrated the chemoselectivity of this method, since the benzylic methyl substituent as well as the unprotected alcohol remained unaffected. However, amino functionalities as in 4-aminophenylacetic acid **294p** were not tolerated and resulted in complex mixtures that showed signals in the range of δ = 10 ppm in the ^{1}H NMR spectrum,

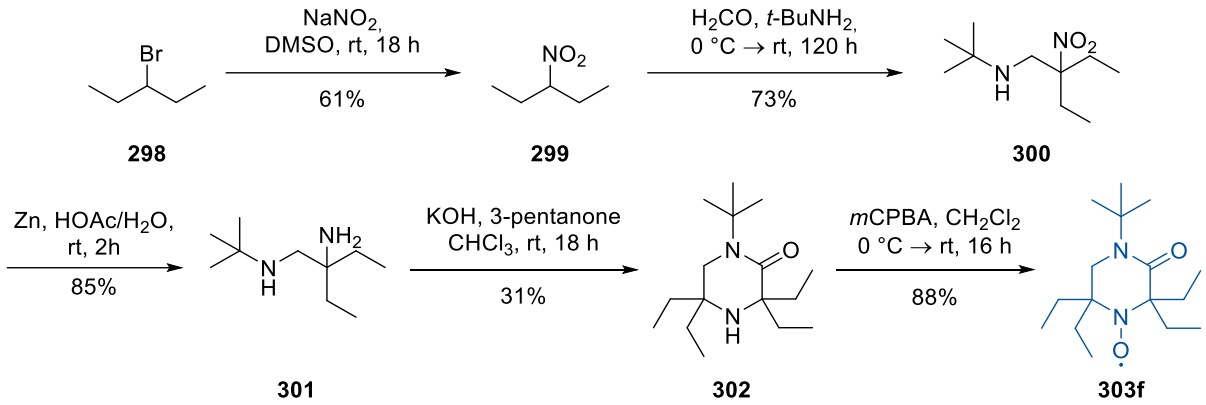
indicating the presence of aldehydes and/or imines. The method was also suitable for the preparation of TEMPO esters from α-keto acids such as **294l**. In nature, similar oxidative decarboxylations exist in nature, e.g. the conversion of *α*-ketoglutarate to succinyl-CoA catalyzed by the oxoglutarate dehydrogenase complex as part of the citrate cycle.[198] Finally, the decarboxylations were carried out on two more complex acids, namely indomethacin **294n** and ibuprofen **294o**, which gave the alkoxyamines **293n** and **293o** in moderate to good yields. When acids without aryl moieties, such as 1-adamantanecarboxylic acid **294h** and cyclohexanecarboxylic acid **294i**, were applied, the formation of the desired alkoxyamines was detected only in trace amounts. Just as with the firstly optimized method, mainly non-decarboxylative C-H activations were observed in various positions within the alkyl backbone.[141]



Scheme 78 Substrate scope of the radical decarboxylative aminoxylation.

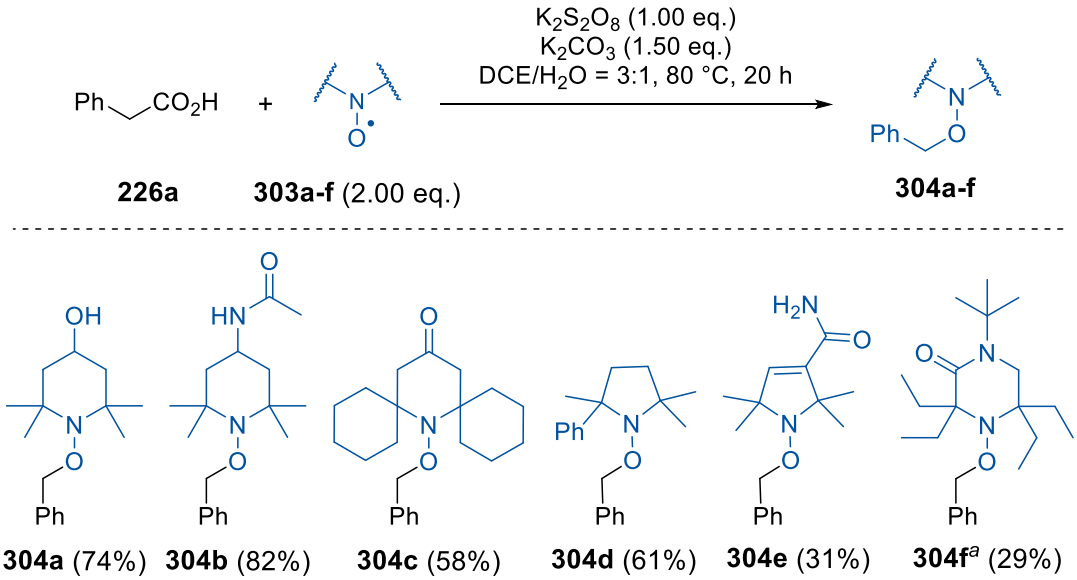
The next step was investigating the substrate scope with respect to the aminoxyl radicals. In the application of alkoxyamines in nitroxide-mediated polymerizations and in cyclization reactions in synthetic organic chemistry, the structure of the aminoxyl radicals plays an important role.[130] Both the dissociation and recombination rates of the C-O bond, whose homolytic cleavage initiates the radical cross-coupling reaction cascade, depend significantly on the structure of the aminoxyl radical. This concerns the ring size, the steric size as well as the polarity of the persistent radical.[199]

In total six structurally versatile aminoxyl radicals were tested in the decarboxylative aminoxylation of phenylacetic acid (**226a**). 4-Hydroxy-TEMPO (**303a**) and 4-acetamido-TEMPO (**303b**) were commercially available and **303c-e** were synthesized as part of a master's thesis project.[182] The complex aminoxyl radical **303f** was prepared according to a procedure reported by STUDER *et al.* starting from 3-bromopentane **298** (Scheme 79).[200]



Scheme 79 Synthesis of aminoxyl radical **303f**.

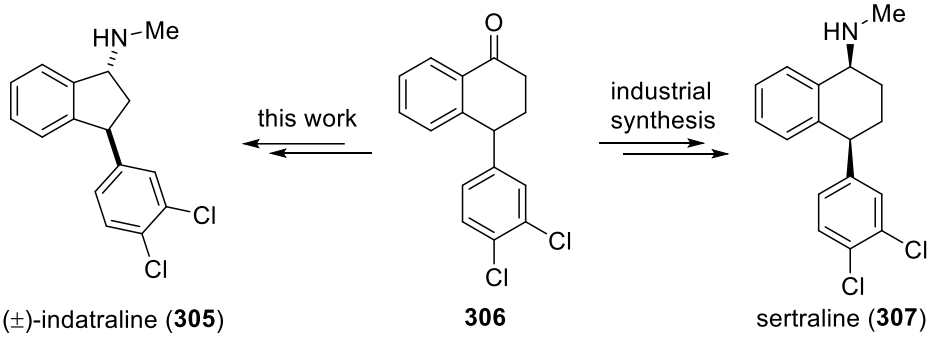
As shown in Scheme 80, applying TEMPO derivatives **303a-c** and 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL)-type radicals **303d** and **303e** the corresponding alkoxyamines could be obtained in low to good yields. Compound **304f** was isolated in only 29% yield, probably due to the low stability of the product at elevated temperatures.



Scheme 80 Use of other aminoxyl radicals **303a-f** in oxidative decarboxylations with phenylacetic acid (**226a**); [a] **304f** turned out to be instable at elevated temperatures.

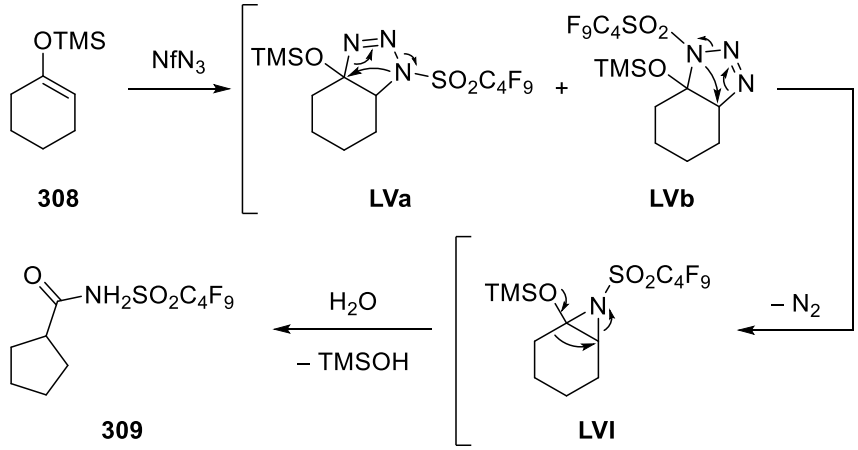
To demonstrate the synthetic advantages of the novel methodology, an application in the context of a total synthesis was targeted. A suitable candidate for this purpose is indatraline (Lu 19-005, **305**), a non-selective inhibitor of the monoamine transporter. It is able block the reuptake of dopamine, norepinephrine and serotonin with effects similar to cocaine, but with a slower onset and longer duration of action. It is therefore a promising candidate for the treatment of cocaine addicts.[201] In addition, indatraline (**305**) is used to block the effects of methamphetamine and MDMA.[202]

Sertraline (**307**), a structurally very similar drug, is one of the best-selling antidepressant and the 14th most commonly prescribed drug in the United States with over 38 million prescriptions in 2017.[203] Since sertraline (**307**) is produced on a very large scale, a synthesis of (±)-indatraline (**305**) starting from an advanced intermediate **306** of the industrial synthesis of sertraline (**307**) was developed (Scheme 81).



Scheme 81 Advanced intermediate **306** of the industrial sertraline (**307**) synthesis as a starting point for a new total synthesis of (±)-indatraline (**305**).

As initial step of the synthesis, a FAVORSKII-type ring contraction of tetralone **306** was envisaged. In 2013, HERZON and co-workers developed a practical way to achieve this kind of transformation. The transition-metal free protocol for the ring contraction of silyl enol ethers of cyclohexanones is based on a click reaction of the TMS-enolate **308** with nonaflyl azide. Aziridine **LVI** formed by the loss of nitrogen promotes ring contraction upon aqueous workup to give amide **309** (Scheme 82).[204]



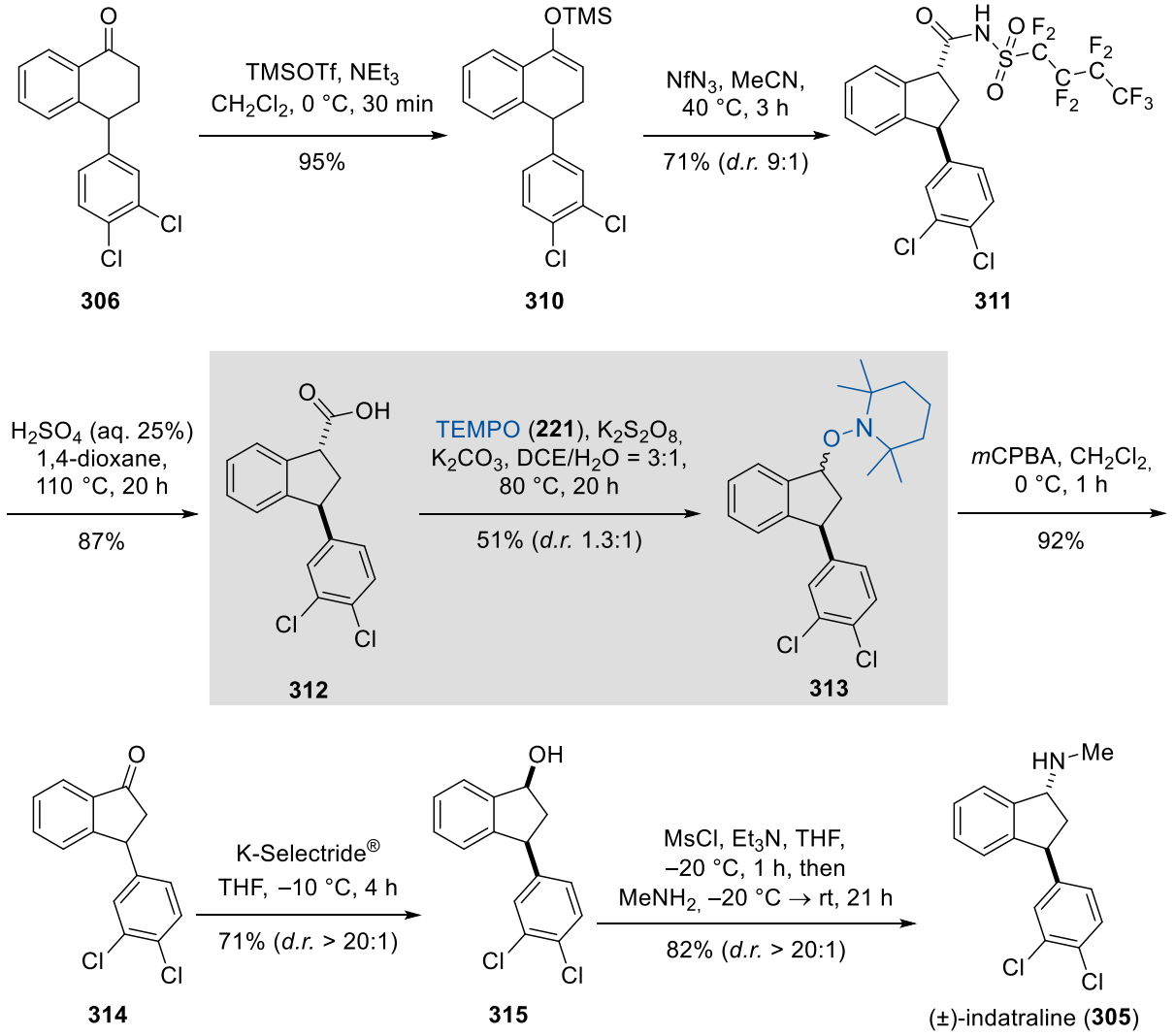
Scheme 82 Proposed mechanism of the transition metal free ring contraction by HERZON *et al.*[204]

A slightly modified variant of this protocol was successfully applied for the new total synthesis approach for (±)-indatraline (**305**) (Scheme 83). Tetralone **306** was first treated with trimethylsilyl trifluoromethanesulfonate and triethylamine to obtain TMS-enol ether **307** in almost quantitative

yield. The subsequent click reaction with nonaflyl azide and the resulting nitrogen-releasing rearrangement led to amide **311** as anti-diastereomer (*d.r.* 9:1) in 71% yield.

At the time of this work, no conditions had been reported for the saponification of nonaflyl amides. Since it was assumed that the strong electron-withdrawing effect of the nonaflyl group could stabilize a negative charge on the nitrogen atom, acidic conditions were attempted. By stirring amide **311** in a mixture of aqueous sulfuric acid in 1,4-dioxane at 100 °C, carboxylic acid **312** was obtained in 87% yield.

Subsequently, the newly developed radical decarboxylative aminoxylation was employed to remove the excess carbon atom while incorporating an oxygen functionality. The reaction succeeded under the optimized conditions, allowing the alkoxyamine **313** to be collected as a mixture of the diastereomers in a yield of 51%. The following oxidation by *m*CPBA gave indenone **315**. The synthesis was then completed following the established protocols of DAVIES and FROIMOWITZ.[205,206] First, diasteroselective reduction was carried out using K-Selectride®. The resulting *syn*-indenol **315** was finally converted to (±)-indatraline (**305**) by mesylation followed by nucleophilic substitution with methylamine.



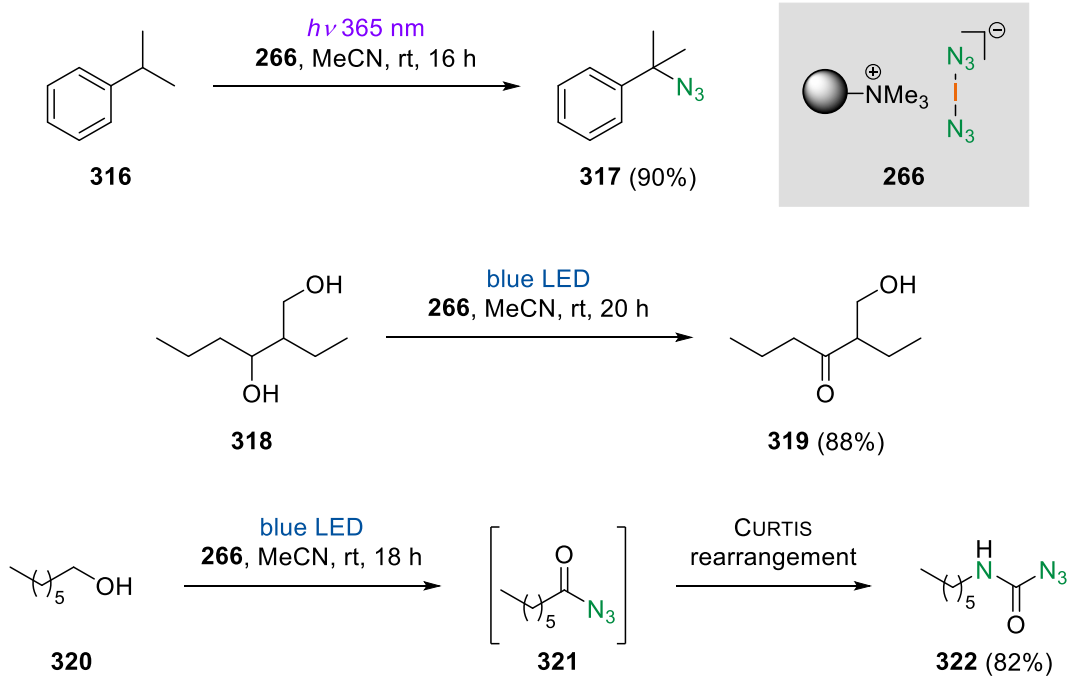
Scheme 83 A new total synthesis approach for (±)-indatraline (**305**) based on the decarboxylative aminoxylation of carboxylic acid **312**.

B3.2 Photochemical Transformations with IN_3 after Release from an Ion-Exchange Resin

In 2017, MUÑIZ and co-workers reported the preparation and reactivity of tetraalkylammonium diacyliodate(I) salts. In great analogy to the work of KIRSCHNING *et al.* from the late 1990s (c.f. Section B1.5), they applied the reagents for the vicinal iodooxygenation of alkenes following an ionic mechanism. Moreover, the study confirmed the linear structure of the anionic iodate(I) complexes by X-ray analysis.[207]

This work inspired KIRSCHNING's group to resume research in the field of iodine(I) chemistry. Thereby, the focus was set on the polymer-bound variant **266** of the bis(azido)iodate(I) complex which was previously applied for ionic iodoazidations of olefins (Scheme 69).[177] Assuming that this halogen(I) species have a similar repertoire of reactivity as hypervalent iodine(III), several test reactions were carried out by KÖSEL using Amberlyst® A-26-bound iodine azide **266**.[208]

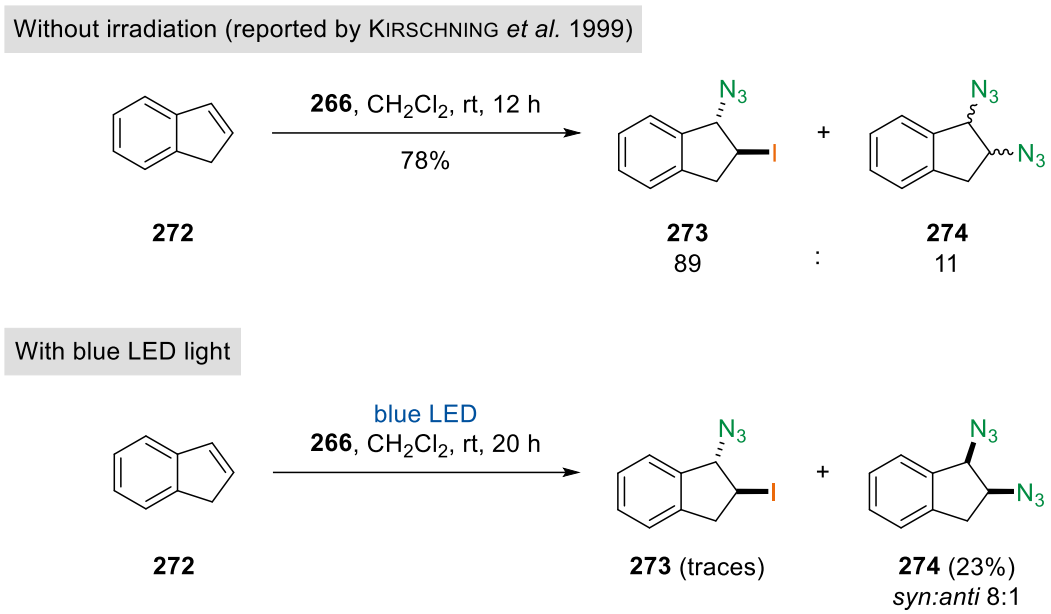
Under photochemical conditions, C-H activations and oxidations were observed that had not been described before (Scheme 84). Such as the azidation at the benzylic position of compound **316** under UV light irradiation.[208] Of particular interest was the selective oxidation of secondary alcohols in the presence of primary alcohols using blue LED light. Primary alcohol **320** reacted much more sluggishly towards the instable acyl azides **321**, which underwent CURTIS rearrangement and a second azidation to yield the corresponding carbamoylazide **322** [209]



Scheme 84 Recently disclosed reactions using the polymer-bound iodine azide **266**.[208,209]

Since the oxidations of alcohols **318** and **320** were successful only under photochemical conditions, it was reasonable to propose a radical mechanism initiated by the homolytic cleavage of iodine azide released from ion-exchange resin **266**. To prove this hypothesis, **266** was exposed to blue LED light (λ_{max} = 445–510 nm) in the presence of indene (**272**). Under these conditions the *syn*-bisazido adduct **274** was predominantly formed (Scheme 85). The MARKOVNIKOV-type-iodoazidation product **273**, reported by KIRSCHNING *et al.* as major product of the same transformation without irradiation,[177] was observed only in trace amounts. The formation of the *anti*- MARKOVNIKOV product, which would

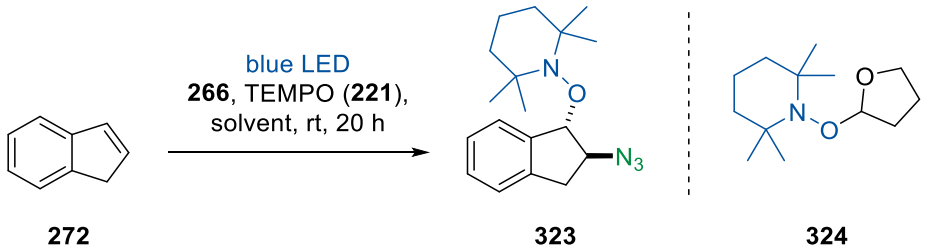
certainly confirm a radical mechanism, could not be observed. However, this might be explained by the fact that C-I bonds can be readily cleaved upon irradiation, especially if this leads to a well-stabilized radical as would be the case here.[210]



Scheme 85 Reaction of polymer **266** and indene (**272**) with and without blue light irradiation.

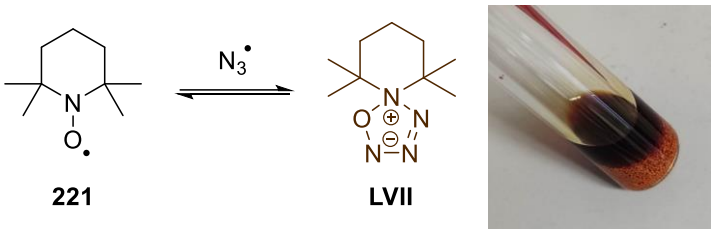
To gather further evidence for the presence of a radical process, TEMPO (**221**) was added to the reaction mixture as a radical scavenger (Table 19). This resulted in the formation of the *anti*-1,2-adduct **323**. The solvent used had only a minor influence on the result of the reaction. However, the formation of the oxidized furan **324** was detected when using THF. In the absence of indene (**272**), THF adduct **324** was isolated in 91% yield. Similar radical H-abstractions of tetrahydrofurans and other heterocycles by azide radicals generated from $PhI(OAc)_2$ and sodium azide have already been described by GREENBERG.[211]

Table 19 Radical azidooxygenation of indene **272** using different solvents; structure of TEMPO-THF adduct **324** formed by C-H activation of THF.



Entry	Solvent	Yield / %	Side products
1	CH_2Cl_2	77	n.d.
2	MeCN	59	n.d.
3	DMF	74	n.d.
4	THF	80	**324** (91% in absence of **272**)

If dichloromethane, acetonitrile or dimethylformamide were used, the reaction mixtures rapidly turned dark brown upon irradiation, which was attributed to the formation of a TEMPO-N_3 complex **LVII** (Scheme 86). This type of charge-transfer complexes has already been described for sterically demanding TEMPO derivatives.[212]



Scheme 86 Formation of TEMPO-N_3 complex **LVII** indicated by the dark-brown color of the reaction mixture.

In addition to the color change, mass spectroscopic studies also indicated the formation of complex **LVII**. A sample taken from a reaction mixture of polymer **266** and TEMPO (**221**) in acetonitrile was analyzed by ESI-MS after 2 h under blue LED light. The spectrum (Figure 19) shows signal at m/z = 199.2 $[M+H]^+$ which could be TEMPO-N_3 (**LVII**).

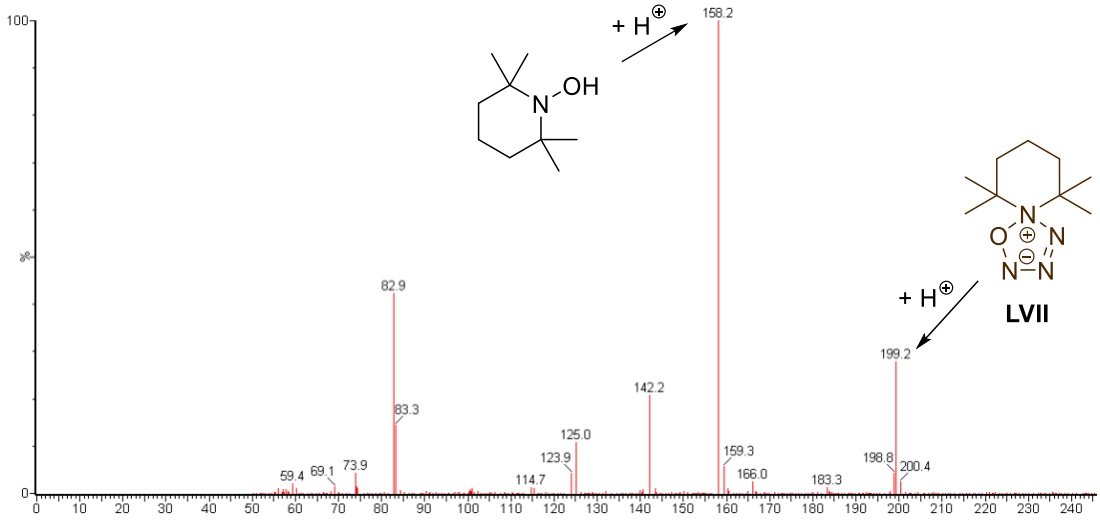


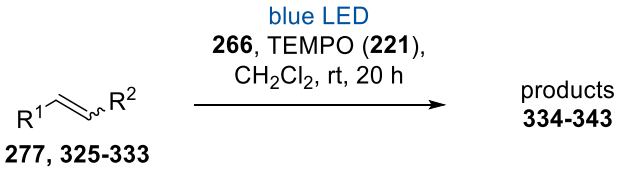
Figure 19 ESI^+ mass spectrum of a mixture of TEMPO (**221**) and polymer **226** in acetonitrile after irradiation with blue LED light.

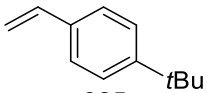
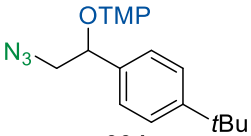
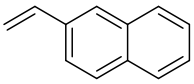
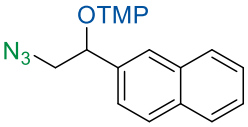
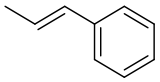
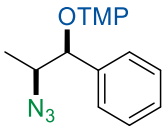
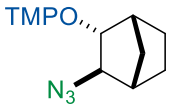
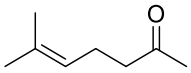
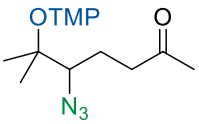
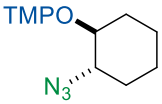
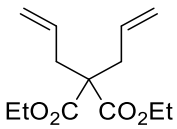
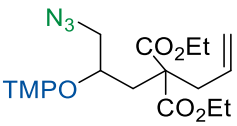
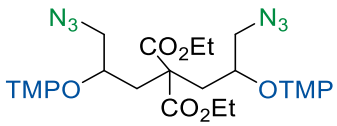
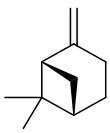
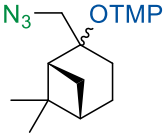
Azidooxygenation of alkenes is a powerful chemical tool for establishing nitrogen and oxygen functions in direct vicinity, a widely distributed structural motif of drugs and natural bioactive compounds.[213] Therefore, the scope of this radical process was extended (Table 20). In the majority of cases, the product of the desired transformation was formed, although the yields varied widely. However, styrene derivatives were generally well accepted (Entries 1 – 3). Remarkably, when 1,2-disubstituted olefins were utilized as substrates, the sterically preferred diastereomer was formed exclusively (Entries 2 – 4, 6). Dien **330** led to a mixture of the di-azidooxygenated product **340a** and the mono-azidooxygenated alkene **340b** (Entry 7). In the cases of the pinenes **331** and **332**, only trace amounts of the desired products **341** and **342** were formed (Entries 8 – 9). Instead, the generation of the ionically iodoazidates products were observed in the ^1H NMR spectra of the crude mixtures.

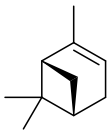
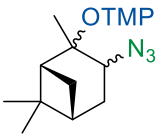
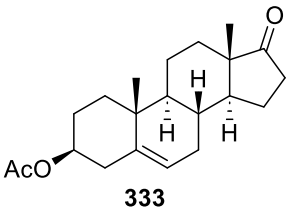
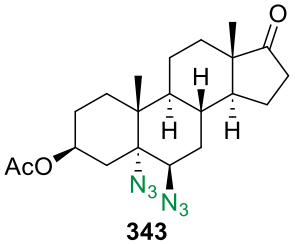
Under the same conditions, 3-(acetoxy)-androst-5-en-17-one (**333**) yielded the *anti*-1,2-bisazido adduct **343** in 50% yield and not the azidooxygenated product (Entry 10). This result is consistent with the observations by LIN and co-workers, who found that aminoxyl radicals are able to catalyze the

anti-diazidation of alkenes, likely with complex **LVII** serving as an azide radical reservoir.[212] This alternative outcome of the reaction is fostered by increasing steric hindrance around the alkene moiety and the aminoxyl radical.[209]

Table 20 Azidooxygenation of **277 and 325-343** by the photochemical activation of polymer-bound reagent **266**.

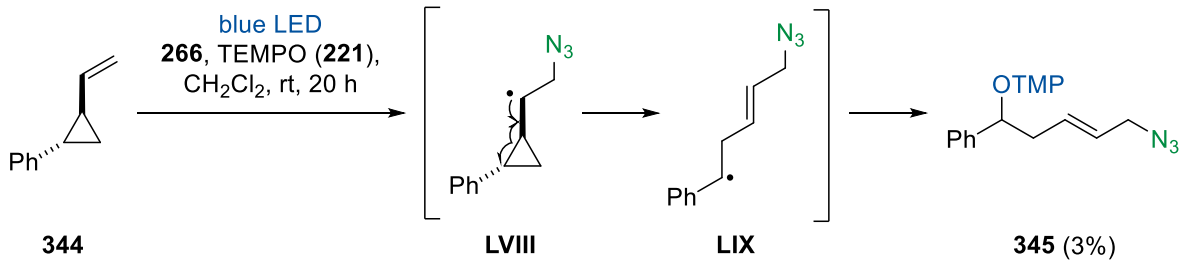


Entry	Substrate	Product	Yield /%
1	 **325**	 **334**	67
2	 **326**	 **335**	45
3	 **327**	 **336**	49
4	 **328**	 **337**	51
5	 **329**	 **338**	53
6	 **277**	 **339**	4
7[a]	 **330**	 **340a**  **340b**	**340a** 35 **340b** 6
8	 **331**	 **341**	traces

9	 **332**	 **342**	traces
10	 **333**	 **343**	50

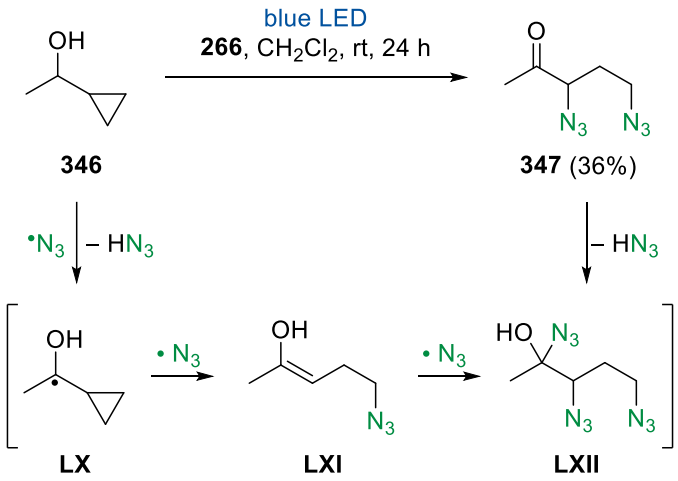
[a] reaction was carried out in MeCN for 5 days

Another method to prove the radical nature of a transformation are radical clock reactions. Radical clocks are chemical compounds that undergo unimolecular radical reactions, typically cyclizations or ring-opening reactions.[214] In this case, vinyl cyclopropane **344** served as the starting material (Scheme 87). The formation of the ring-opened allyl azide **345** was observed albeit in a very low yield.



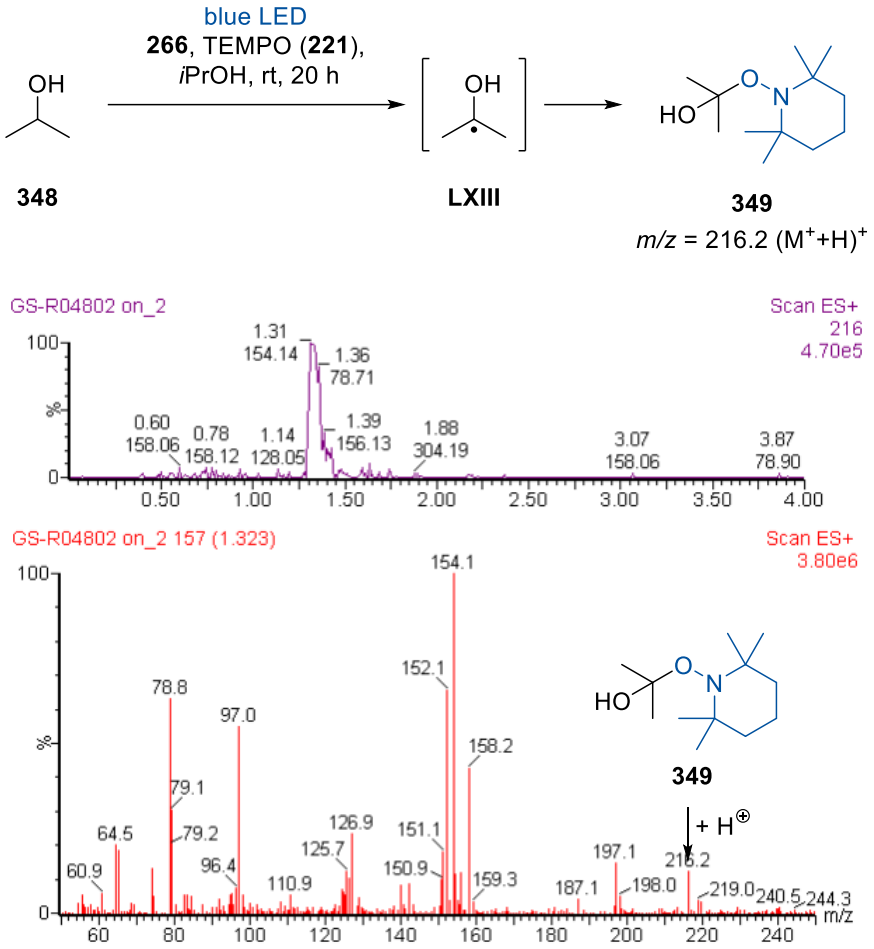
Scheme 87 Radical clock experiment using vinyl cyclopropane **344**.

In order to verify that the chemoselective oxidation of secondary alcohols observed by KÖSEL is also based on single-electron processes, a second radical clock reaction was carried out (Scheme 88). Treatment of 1-cylcopropyl ethanol (**346**) under the conditions optimized for the oxidation of secondary alcohols by KÖSEL yielded bisazide **347**. This result provides evidence that a ketyl radical **LX** must have been generated as an intermediate, which led to the formation of bisazide **347** by subsequent reactions via **LXI** and **LXII**.



Scheme 88 Radical clock reaction of 1-cyclopropylethanol (**347**), which provides evidence for the formation of a ketyl radical **LX** during alcohol oxidation.[209]

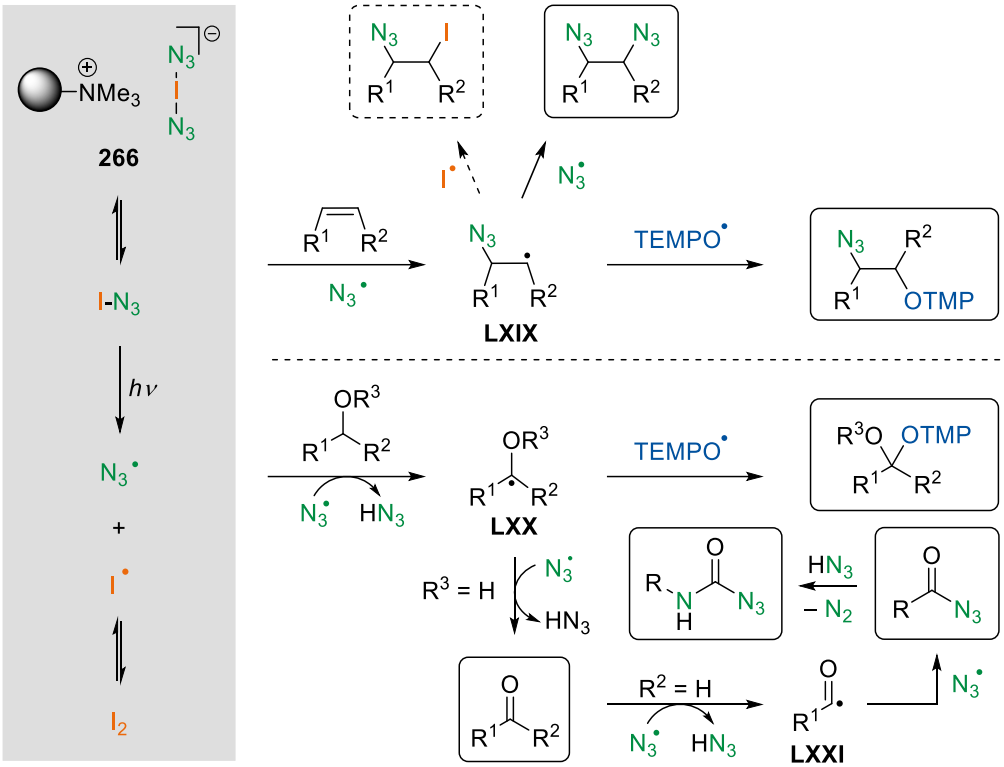
Subsequently, attempts were made to scavenge the intermediary ketyl radical. Therefore, polymer-bound reagent **266** in *i*PrOH (**349**) was treated with TEMPO and irradiated with blue LED light for 20 h. Detailed mass spectrometric studies (LC/MS) of the crude reaction mixture were carried out. These displayed a signal at m/z = 216.2 $[M+H]^+$ indicative for TEMPO adduct **349**, which, however, could not be isolated (Scheme 89).



Scheme 89 Trapping of the ketyl radical (**LXIII**) by TEMPO (**221**) provides hemiacetal **350** as detected by LC/MS analysis. Chromatogram for the specifies mass (m/z = 216) and ESI^+ mass spectrum at the time of highest intensity are shown.

Based on the collected results, the mechanistic Scheme 90 can be summarized. Polymer-bound iodate(I) complex **266** provides iodine azide, which under photocatalytic conditions undergoes homolytic cleavage to yield the azide and iodine radical. The latter can readily recombine to form molecular iodine. The azide radical is able to add to alkenes and the newly formed radical **LXIX** can be trapped by iodine or azide radicals or by TEMPO (**221**).

The azide radical also enforces C–H abstraction next to a C–O bond such as in tetrahydrofuran or alcohols. In the former example this was proven by isolation of the TEMPO adduct **324**, while in the second case the corresponding ketones formed from secondary alcohols via ketyl radicals **LXX**. Primary alcohols also form intermediate **LXX** but the resulting aldehyde undergoes a second C–H abstraction to yield acyl radical **LXXI**. This is trapped by an azide radical to yield acyl azides, which may undergo the CURTIUS rearrangement with final addition of HN_3 to form the corresponding carbamoylazides.[209]

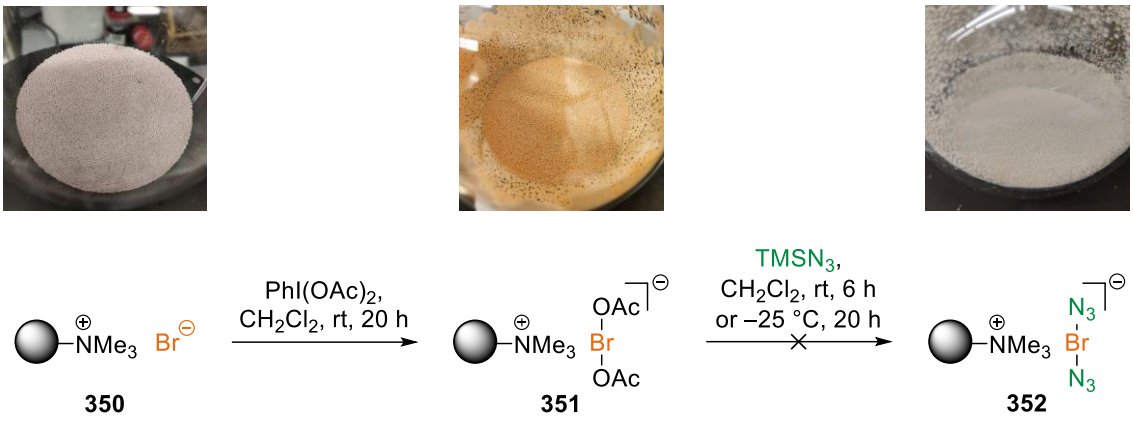


Scheme 90 Proposed mechanistic considerations for radical processes with polymer-bound iodine azide **266**.[209]

B3.3 Taming Bromine Azide for the Use in Organic Solvents

Encouraged by the results obtained with the polymer-bound bis(azido)iodate(I) complex **266**, the question arose if similar results could also be obtained with a bromate(I) analogue of this species. As explained in Section B1.5, the low polarization of the Br–N_3 bond ensures that bromine azide, in contrast to iodine azide, tends to exhibit the character of a free radical reagent. It was therefore hypothesized that by substituting polymer **266** with an equivalent bromine species, problems arising from ionic side reactions would be minimized. This would result in a higher efficiency for the desired radical transformations.

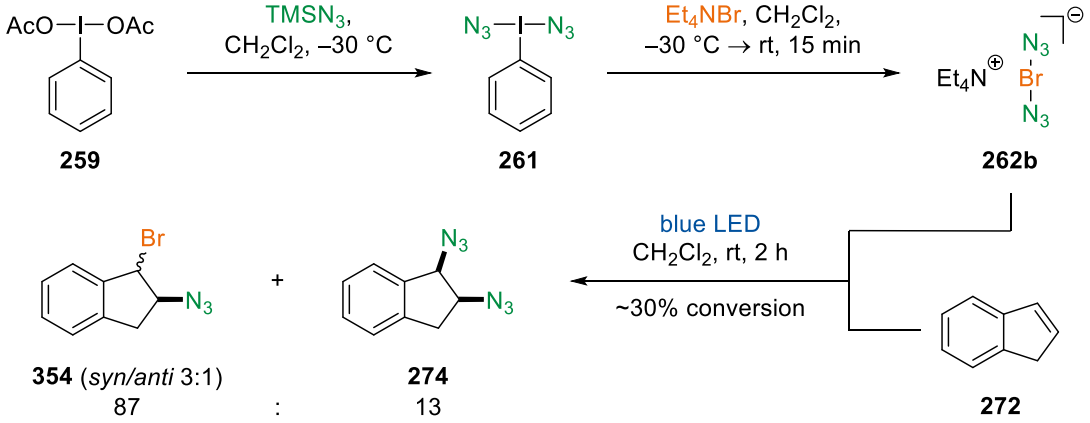
In order to verify this conclusion, attempts were made to prepare bis(azido)bromate(I) complex **352** starting from the bromide form of Amberlyst® A26 resin **350** (Scheme 91). The polymer-supported bis(acetoxy)bromate(I) anion **352** has already been described in 2003 by KIRSCHNING *et al.*[215] The preparation of the yellow polymer was successfully reproduced. The ligand exchange using trimethylsilyl azide under the established conditions for the bis(azido)iodate(I) species **266** resulted in a gas evolution and decolorization of the resin. The resulting polymer was tested by adding it to a solution of TEMPO (**221**) in CH_2Cl_2 followed by irradiation using blue LED light, which should lead to the release of azide radicals thereby forming the brown TEMPO-N_3 complex **LVII** (Section B3.2, Scheme 86). However, no color change was observed. Similarly, no transformation was found in the reaction with indene (**272**) under the conditions established for the IN_3 species **266**. It was therefore concluded that the bromine azide polymer **352** did not form successfully or was unstable at room temperature. Therefore, the ligand exchange and the test reactions were carried out again at a reduced temperature of −25 °C. In this case, the addition of trimethylsilyl azide initially led to an orange coloration of the polymer, as is also the case for the corresponding iodinate(I) species. However, after a few minutes, decolorization occurred and the test reactions showed no signs of azide radical release.



Scheme 91 Attempted preparation of bis(azido)bromate(I) complex **352**.

The problem could be linked to the backbone structure of the resin. Amberlyst® A-26 is a crosslinked styrene-divinylbenzene copolymer that possesses benzylic C–H bonds which might be activated by azide radicals.[216] Although this reactivity was not observed with polymer-bound iodine azide **266**, it cannot be completely ruled out that in the presence of a higher concentration of azide radicals such side reactions could occur and therefore lead to the decomposition of the polymer.

Alternatively, it was investigated whether the desired radical transformations can be obtained with the *in situ* prepared tetraethylammonium salt **262b**. This species has already been described in 1999 by KIRSCHNING's group as an efficient reagent for ionic bromoazidations (Scheme 68, Section B1.5).[176] In accordance with the literature, **262b** was prepared from (diacetoxyiodo)benzene (**259**), trimethylsilyl azide and tetraethylammonium bromide at –30 °C in dichloromethane (Scheme 92). Upon subsequent warming to room temperature, strong gas evolution was observed. Indene (**272**) was then added and the mixture was irradiated with blue LED light. Since no further conversion of the starting material was observed after two hours, the reaction was terminated. Subsequent analysis of the crude reaction mixture by ^{1}H NMR analysis revealed that both diastereomers of the desired bromoazidated compound **354** and *syn*-diazido compound **274** were formed. However, only a low conversion of the starting material was observed, although arithmetically three equivalents of the bromate(I) salt **262b** should have been generated.

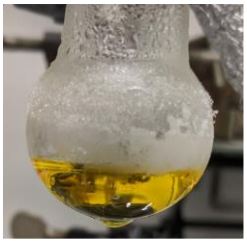


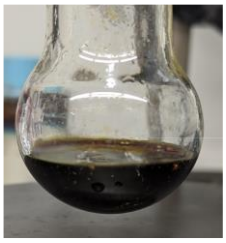
Scheme 92 First attempt for the radical bromoazidation of indene (**272**) using *in situ* generated tetraethylammonium bis(azido)bromate(I) (**262b**).

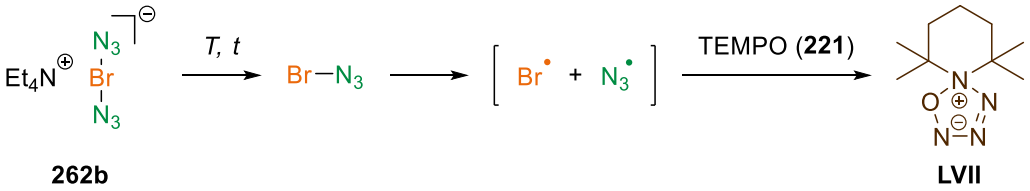
Based on these initial results, it was assumed that the stability of the bromate(I) complex is relatively low and therefore most of the active species had already been released prior to the addition of indene (**272**). Homolysis of bromine azide than occurred, leading to the formation of bromine and azide radicals. At high concentrations of the radicals, their recombination is more likely, yielding molecular bromine and N_6, which immediately degrades to nitrogen. This would provide an explanation for the observed gas formation upon warming of the reaction mixture.

To confirm these assumptions, the temperature stability of tetraethylammonium bis(azido)bromate(I) (**262b**) was studied by GEORGE. For this purpose, the complex was prepared at −35 °C, then TEMPO (**221**) was added, and the solutions were allowed to warm to the temperatures indicated in Table 21. The time until the formation of the brown TEMPO-N_3 complex **LVII** was measured. At temperatures above 0 °C the bromate(I) complex decomposed almost instantaneously. In contrast, at −16 °C, the color change was observed after 2 minutes. For lower temperatures, irradiation with blue LED light was necessary to observe the desired formation of the charge-transfer complex. At −35 °C, only a very pale brown coloration was observed after 5 minutes of irradiation.[217]

Table 21 Studies on the temperature-dependent stability of the bis(azido)bromate(I) species **262b** by GEORGE.[217]







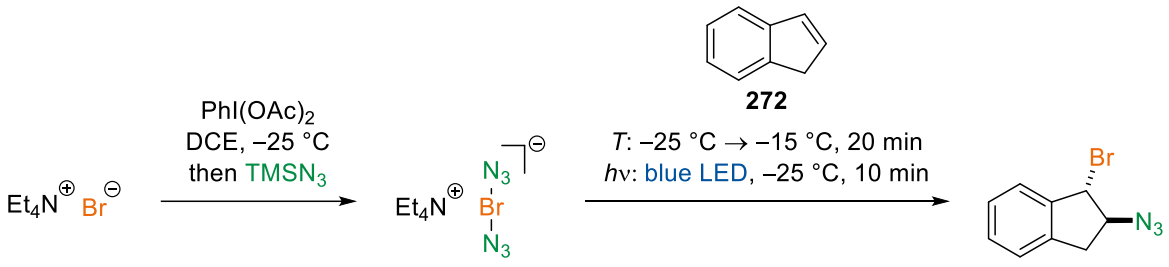
262b **LVII**

Entry	T / °C	gas evolution	t_{change} / s
1	32	++	1
2	0	+	10
3	−16	–	120
4	−25	–	>300, 10[a]
5	−35	–	>300[a]

[a] irradiation with blue LED light

In the next step, GEORGE carried out a reaction series to optimize the conditions for the bromoazidation of indene (**272**). Thereby, 1,2-dichloroethane was applied as solvent, as it led to better results than dichloromethane. Since a slow and controlled release of bromine azide was desired, −25 °C were used for reactions under blue LED light irradiation and −15 °C for transformations without irradiation. To avoid the formation of the highly explosive (diazidoiodo)benzene (**261**), the addition order of the reagents was changed. Tetraethylammonium bromide was initially treated with (diacetoxyiodo)benzene (**259**) before the ligand exchange was carried out using trimethylsilyl azide. The results shown in Table 22 indicate that the desired product was formed even without irradiation. The ratio of reagents had a strong effect on yield, but a marginal influence on the diastereoselectivity. The best results were obtained with the conditions in entry 7 under irradiation with blue LED light.[217]

Table 22 Optimization studies on the bromoazidations of indene (**272**) by GEORGE.[217]

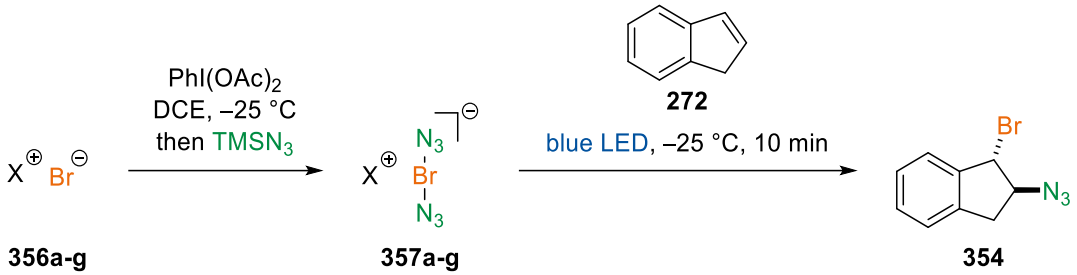


Entry	Et_4NBr /eq.	$PhI(OAc)_2$ / eq.	$TMSN_3$ /eq.	Method	*trans*:*cis*[a]	Yield[b] / %
1	1.50	2.00	4.00	*T*	n.d.	(63)
2	1.50	2.00	4.00	*hν*	n.d.	(62)
3	3.00	5.00	8.00	*hν*	n.d.	(42)
4	3.00	5.00	8.00	*T*	n.d.	(61)
5	1.50	2.00	4.00	*hν*	8:1	65
7	2.00	1.50	3.50	*hν*	9:1	79 (74)
8	3.00	1.50	2.80	*hν*	8:1	65 (63)
9	2.00	1.50	3.50	*T*	8:1	63 (62)

[a] Determined by ^{1}H-NMR spectroscopy; b ^{1}H NMR-yields of the trans-product using naphthalene as an internal standard; yields in brackets are isolated yields.

Finally, the influence of the counterion of the bis(azido)bromate(I) anion was investigated by GEORGE (Table 23). Improved yields and diastereoselectivities were obtained when the bromide was less soluble in DCE (relative yields: Oct_4N^+ < Bu_4N^+ < Et_4N^+ < Et_4P^+). However, no conversion was observed if the solubility of the bromide source is too low (Me_4N^+ and $Me_2Dod_2N^+$). The best results were achieved using tetraethylphosphonium bromide (**356g**).[217]

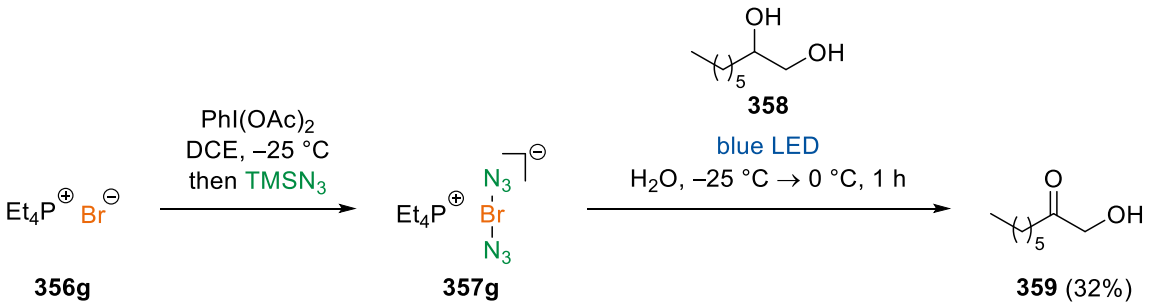
Table 23 Optimization studies on the bromoazidation of indene (**272**) regarding the bromide source by GEORGE.[217]



Entry	X⁺	Yield / %[a]	*trans*:*cis*[b]
1	Me_4N^+ (**356a**)	-	-
2	Et_4N^+ (**356b**)	79	9:1
3	Bu_4N^+ (**356c**)	47	5:1
4	Oct_4N^+ (**356d**)	53	4:1
5	$Me_2Dod_2N^+$ (**356e**)	-	-
6	Et_4P^+ (**356g**)	86	10:1

[a] ^{1}H NMR-yields of the *trans*-product using naphthalene as an internal standard; [b] determined using ^{1}H-NMR spectroscopy.

With the optimized conditions in hand, it was investigated whether a chemoselective oxidation of secondary alcohols as observed with the polymer-bound iodine azide **266** could also be accomplished with bromate(I) salt **357g**. Since the mechanism proposed in Scheme 90 indicates that two equivalents of the active species are required for oxidation of secondary alcohols, twice the amount of all reagents was employed. Unfortunately, only the *O*-silylation of both hydroxy groups by trimethylsilyl azide was observed. The addition of a few drops of water prevented this side reaction. However, for this purpose it was necessary to increase the reaction temperature to 0 °C, which accelerated the release of the bromine azide and led to gas formation. The oxidation of the secondary alcohol **358** occurred with full chemoselectivity, however, the conversion rate was rather low (Scheme 93).

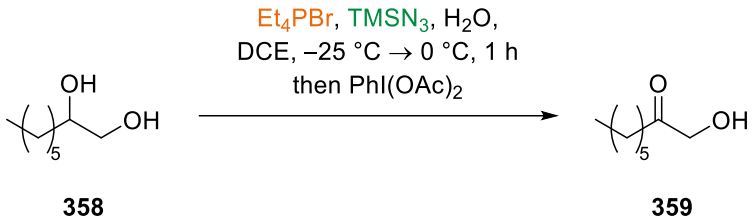


Scheme 93 First attempt for the chemoselective oxidation of diol **358** using *in situ* generated bromine azide.

Therefore, a further optimization series was performed (Table 24). Since intense gas evolution upon irradiation of the reaction mixture at 0 °C indicated that blue LED light leads to an uncontrolled release of the active species at elevated temperatures, the light source was omitted. In an attempt to reduce the likelihood of recombination, the alcohol was pre-stirred with the bromide **356g**, trimethylsilyl azide and water, followed by the portionwise addition of (diacetoxyiodo)benzene (**259**) at room temperature. This method yielded 44% of the desired ketone **359** (Entry 1). Interestingly, increasing

the amount of bromide and oxidant resulted in a deterioration of the yield, while using more trimethylsilyl azide and water was generally beneficial until their levels exceeded a threshold (Entries 2–5). It can be assumed that in the presence of abundant water hydrazoic acid is generated, which is even more reactive than trimethylsilyl azide and might also be capable of conducting the ligand exchange. The optimized yield of 51% was obtained with the conditions specified in Entry 9, although large quantities of the starting material remained. Lowering or increasing the temperature did not lead to any further improvement (Entries 10–11).

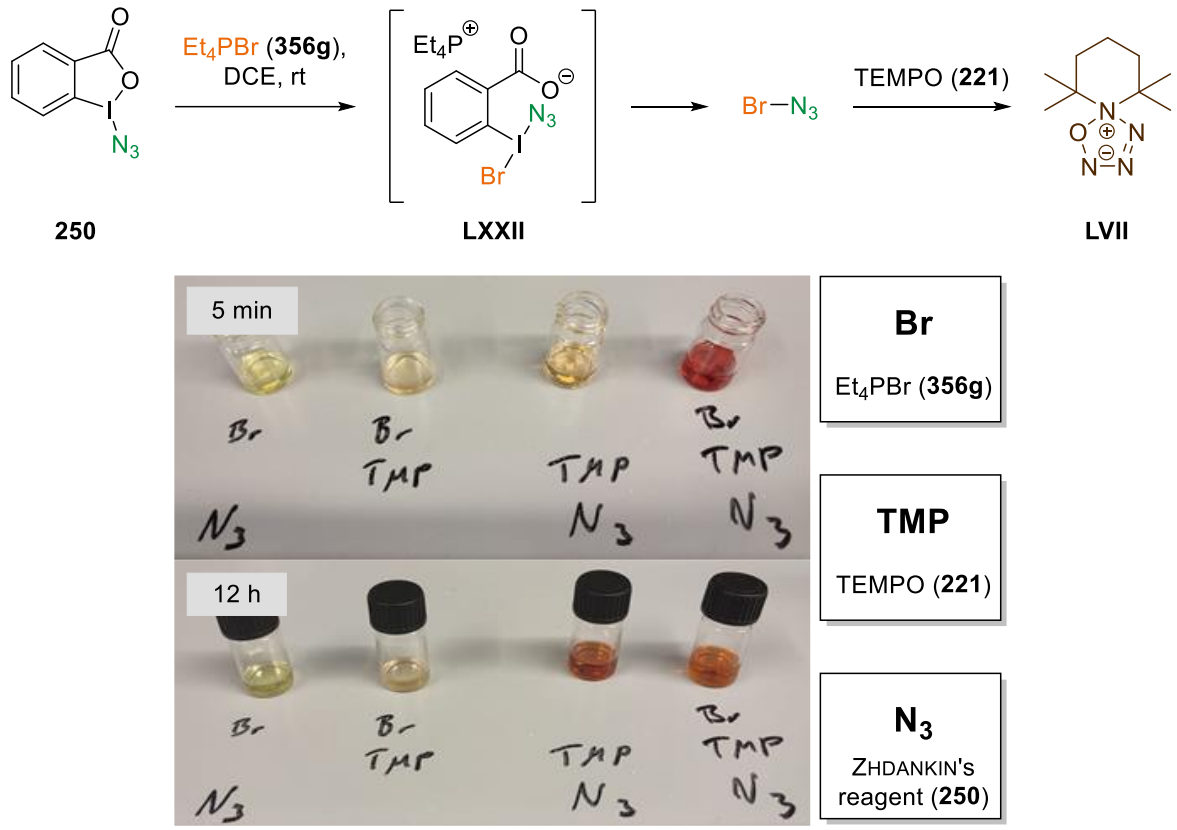
Table 24 Optimization studies on the chemoselective oxidation of diol **358** using *in situ* generated tetraethylphosphonium bis(azido)bromate(I) (**357g**).



358 **359**

Entry	Et_4PBr / eq.	$PhI(OAc)_2$ / eq.	$TMSN_3$ / eq.	H_2O / eq.	T / °C	Yield / %
1	3.00	3.50	6.00	6.00	25	44
2	4.00	6.00	8.00	8.00	25	35
3	2.00	3.00	8.00	8.00	25	48
4	2.00	3.00	10.0	10.0	25	48
5	2.00	3.00	12.0	12.0	25	35
6	2.00	3.00	8.00	2.00	25	12
7	2.00	3.00	8.00	4.00	25	44
8	1.50	3.00	8.00	4.00	25	32
9	2.00	3.00	8.00	40.0	25	51
10	2.00	3.00	8.00	40.0	0	46
11	2.00	3.00	8.00	40.0	60	18

As explained in Section B1.5, bromine azide is known to be very susceptible to hydrolysis.[159] To avoid the addition of water, a TMS-free approach was sought for. A combination of an azide source with oxidative properties was found in the ZHDANKIN's reagent (**250**), which therefore is a valid alternative for the combination of (diacetoxyiodo)benzene (**259**) and trimethylsilyl azide. It was hypothesized that upon addition of bromide anions, iodine(III) species **LXXII** would form, which gives rise to bromine azide by reductive elimination. In 2016, YANG *et al.* demonstrated a similar strategy to generate chlorine azide (Scheme 65, Section B1.5). However, in addition to the ZHDANKIN's reagent (**250**) and the highly reactive thionyl chloride, a copper catalyst was required to achieve product formation.[168] Remarkably, a light yellow coloration and gas evolution could be observed by adding bromide **365g** to a solution of ZHDANKIN's reagent (**250**). By employing TEMPO (**221**), the formation of azide radicals could be verified by means of complex **LVII**. In the absence of bromide **365g**, the formation of azide radicals was also detected, but only after a substantially longer period of time (Scheme 94).



Scheme 94 Bromide-mediated release of azide radicals from ZHDANKIN's reagent.

To verify that bromine azide has formed from the reaction of ZHDANKIN's reagent (**250**) and bromide **365g**, UV-vis spectra of the two reagents were recorded individually and as a mixture in tetrachloromethane (Figure 20). The solution of the mixture turned light yellow indicating the formation of BrN_3. However, the UV-Vis spectrum of the mixture showed the same absorption maximum as the one of the pure iodine(III) reagent **250** (λ_{max} = 273 nm), but with a broadening of the signal into the longer wavelength region.

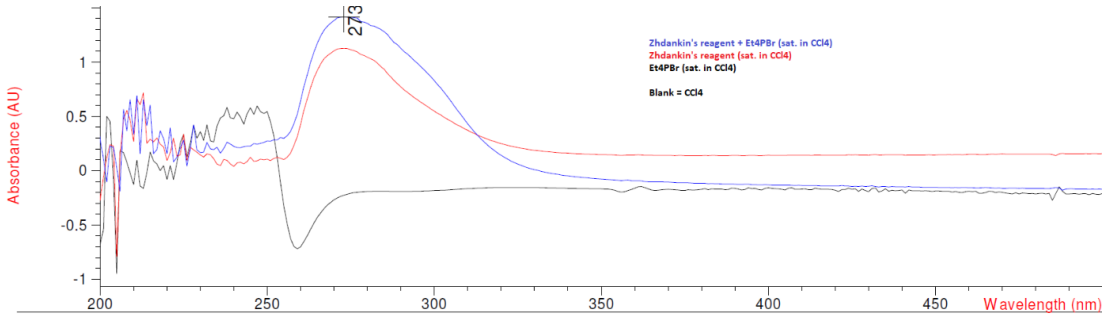


Figure 20 Overlaid UV-vis spectra of Et4PBr (**265g**), Zhdankin's reagent (**250**) and a mixture of both in CCl4.

It can therefore be assumed that the signal from the bromine azide is masked by the absorbance of the ZHDANKIN's reagent (**250**). For this reason, a difference spectrum was recorded with a solution **250** reagent as blank and the mixture of both reagents as sample (Figure 21b). The detected absorption maximum at λ_{max} = 292 nm is in accordance with the literature (λ_{max} = 291 nm) for bromine azide in tetrachloromethane.[218] It has to be noted that the second reported absorption maximum at 420 nm, which has been described in the literature as much less intense, could not be detected.

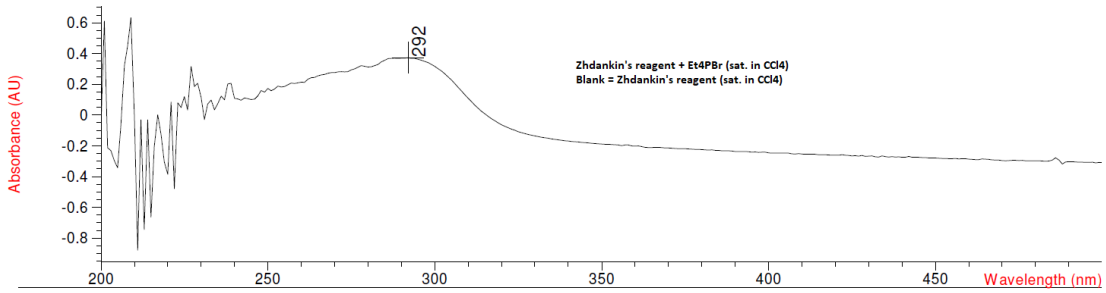
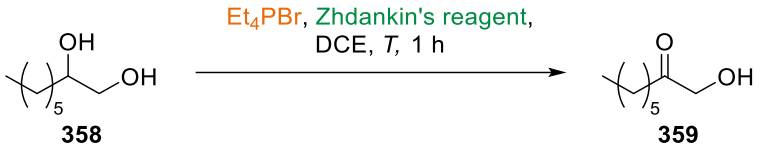


Figure 21 Difference spectrum of ZHDANKIN's reagent (**250**) and the mixture of ZHDANKIN's reagent (**250**) and Et_4PBr (**265g**) in CCl_4.

This new method of generating bromine azide in hand allowed for a final optimization series, which is shown in Table 25. By using one equivalent of bromide **356g** and one and a half of reagent **250**, a yield of 39% was obtained (Entry 1). Adjusting the equivalents improved this significantly to 65% (Entry 4). The identical yield could also be obtained with a smaller excess the reagents by heating the reaction mixture to 50 °C directly after the addition of the components (Entry 11). With NBS as bromine source, the reaction was also successful, but in lower yield after significantly longer reaction time (Entry 13). The addition of copper(I) chloride did not significantly change the result (Entry 14). By reducing the temperature to −25 °C and irradiating with blue LED light, an optimized yield of 69% was obtained (Entry 15).

Table 25 Optimization studies on the selective oxidation of secondary alcohols using ZHDANKIN's reagent (**250**) and Et_4PBr (**365g**).



358 **359**

Entry	ZHDANKIN's reagent / eq.	Et_4PBr / eq.	T / °C	Additive	Yield / %
1	1.50	1.00	25	-	39
2	3.00	2.00	25	-	54
3	4.50	3.00	25	-	64
4	6.00	4.00	25	-	65
5	3.00	3.00	25	-	38
6	4.50	2.00	25	-	52
7	4.50	4.50	25	-	45
8	4.50	3.00	0	-	61
9	4.50	3.00	−10	-	59
10	6.00	4.00	0 ⟶ 25	-	54
11	4.50	3.00	25 ⟶ 50	-	65
12	6.00	4.00	0 ⟶ 50	-	61
13[a]	6.00	-	25	NBS (4.00 eq.)	41
14	4.50	3.00	25 ⟶ 50	CuCl (5 mol%)	60
15[b]	6.00	4.00	−25	-	69

[a] 24 h instead of 1 h reaction time; [b] irradiation with blue LED light.

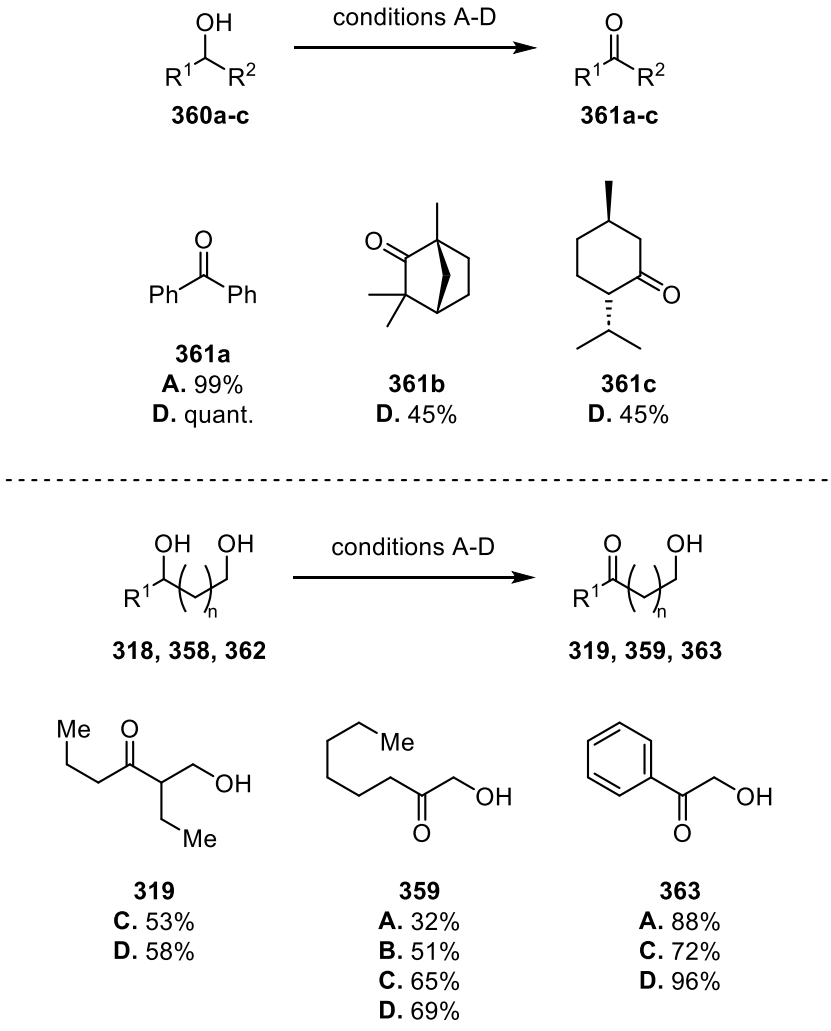
In order to compare the optimized conditions described in this section, a small set of commercially available secondary alcohols **360a-c** and diols **318** and **363** were employed (Scheme 95). In general, the best results were obtained with the photolytic conditions using ZHDANKIN's reagent (**250**) (Condition D). In the case of activated secondary alcohols such as **360a** and **362**, the oxidations proceeded in near quantitative yield. In contrast, the non-activated secondary alcohols **360b** and **360c** are less suitable for these chemoselective oxidations from a preparative point of view.

Conditions A (photolytic)
Et_4PBr (3.50 eq.), $PhI(OAc)_2$ (3.00 eq.), DCE, –25 °C, 0.5 h, then $TMSN_3$ (6.00 eq.), H_2O (6.0 eq.), –25°C → 0 °C, then addition of alcohol, 1 h, blue LED.

Conditions B (thermal)
alcohol, Et_4PBr (2.00 eq.), $TMSN_3$ (8.00 eq.), H_2O (40.0 eq.), DCE, rt, then addition of $PhI(OAc)_2$ (3.00 eq.), 1 h.

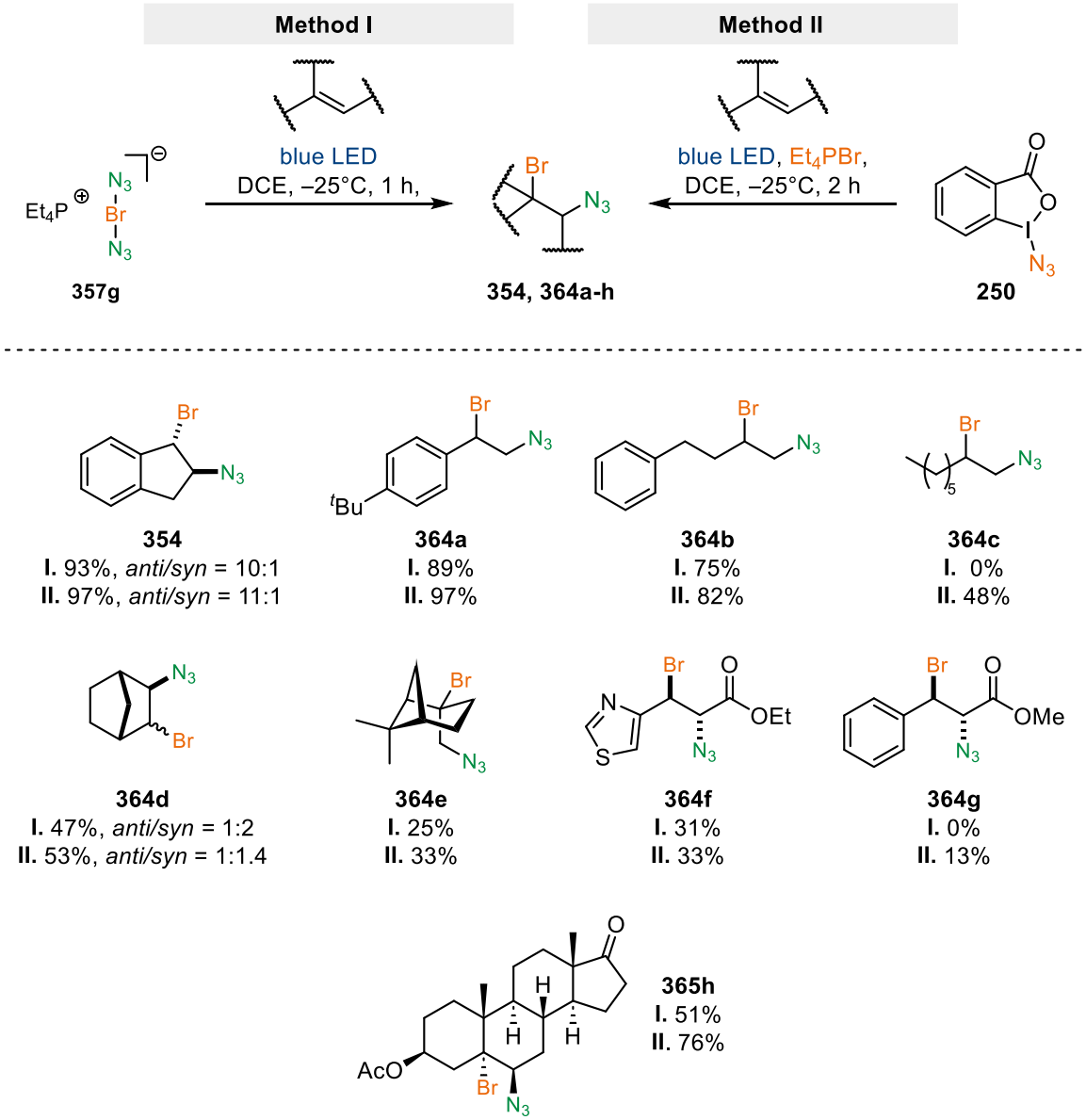
Conditions C (thermal)
ZHDANKIN's reagent (4.50 eq.), Et_4PBr (3.00 eq.), DCE, rt → 50 °C, 1 h.

Conditions D (photolytic)
ZHDANKIN's reagent (6.00 eq.), Et_4PBr (4.00 eq.), DCE, –25 °C → 0 °C, 1 h, blue LED.



Scheme 95 Oxidation of secondary alcohols **360a-c** and diols **319**, **359** and **363** using *in situ* generated bromine azide.[170]

At the same time, GEORGE and TASER investigated the use of the two photolytic methods for the radical bromoazidation of a variety of alkenes (Scheme 96). In cases where a well stabilized radical was formed as an intermediate, good to excellent yields were obtained. However, a series of non-activated olefins were also successfully converted. In general, the yields employing the method based on ZHDANKIN's reagent were significantly higher than those obtained with the bis(azido)bromate(I) complex prepared *in situ*. The formation of bromoazidated compounds **364c** and **364g** could only be observed via Method II.[217]

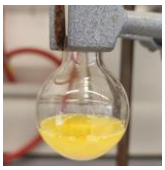


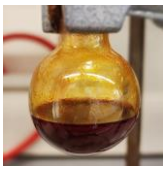
Scheme 96 Radical bromoazidations of alkenes based on bis(azido)bromate(I) complex **357g** (Method I.) and ZHDANKIN's reagent (**250**) (Method II.) carried out by GEORGE and TASER.[170,217,219]

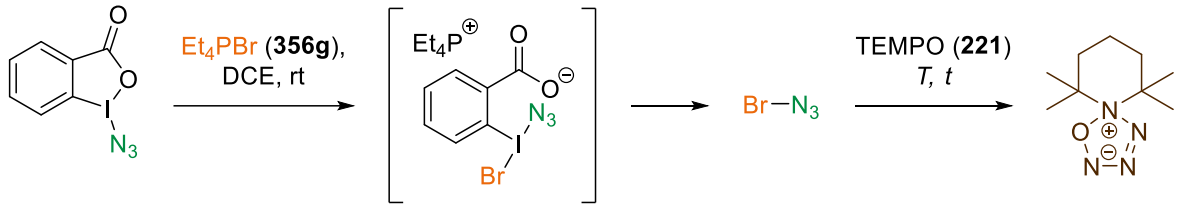
Since it was observed by TASER that transformations were generally faster using the bromate(I)-based method, it was assumed that the release of bromine azide from the reaction of ZHDANKIN's reagent (**250**) and bromide **356g** proceeded in a more controlled manner. To evaluate the hypothesis, the temperature stability experiments that GEORGE had previously performed with tetraethylammonium bis(azido)bromate(I) (Table 21) were repeated with a mixture of ZHDANKIN'S reagent (**250**) and bromide **356g**. The times measured for the appearance of the brown color due to

the formation of charge transfer complex **LVII** were consistently longer. It can therefore be assumed that a slower release of the active ingredient was the main reason for the improved results using the method based on ZHDANKIN'S reagent (**250**). Therefore, it is reasonable to assume that slower release of the active reagent was the main reason for the improved results with the benziodoxolone-based method.

Table 26 Studies on the temperature-dependent release of azide radicals from a mixture of ZHDANKIN'S reagent (**250**) and bromide **356g** in comparison to the data obtained for $Et_4NBr(N_3)_2$ (**262b**) by GEORGE.[217]







250 **LXXII** **LVII**

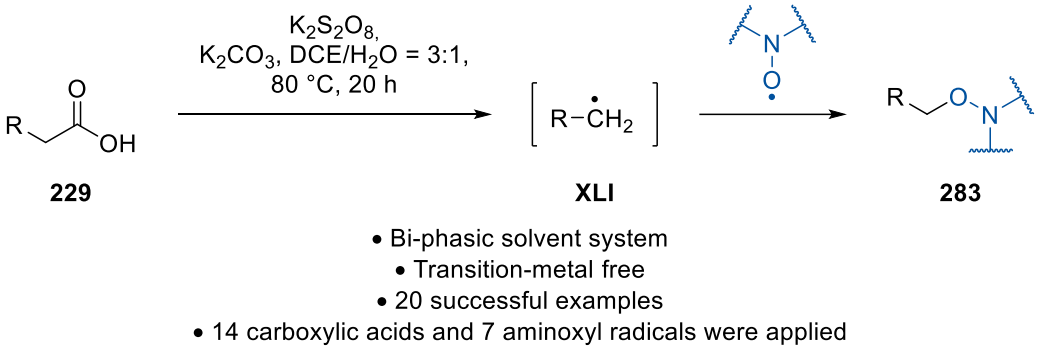
Entry	T / °C	$Et_4NBr(N_3)_2$[217]		ZHDANKIN's reagent + Et_4PBr	
		gas evolution	t_{change} / s	gas evolution	t_{change} / s
1	32	++	1	+	1
2	0	+	10	–	35
3	–16	–	120	–	180
4	–25	–	>300, 10[a]	–	>300, 150[a]
5	–35	–	>300[a]	–	>300[a]

[a] irradiation with blue LED light

B4 Conclusions and Future Work

Within this sub-project of the present dissertation, novel methodologies on three different topics in the field of radical chemistry were developed and their underlying mechanisms were elucidated in detail.

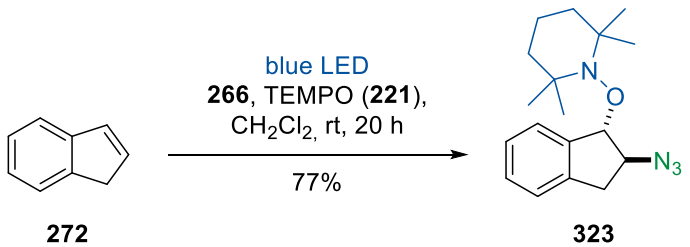
In the first part, a new method for the synthesis of alkoxyamines starting from carboxylic acids by a MINISCI-type oxidative decarboxylation was developed (Scheme 97). The key to success was the use of a two-phase solvent system to avoid otherwise prevalent side reactions such as the oxidation of TEMPO (**221**) by persulfate. Remarkably, the method does not require transition metal catalysts. Its synthetic relevance was demonstrated by the successful incorporation into a new synthetic approach for the drug candidate (±)-indatraline (**305**).



Scheme 97 Transition-metal free decarboxylative aminoxylation of carboxylic acids.

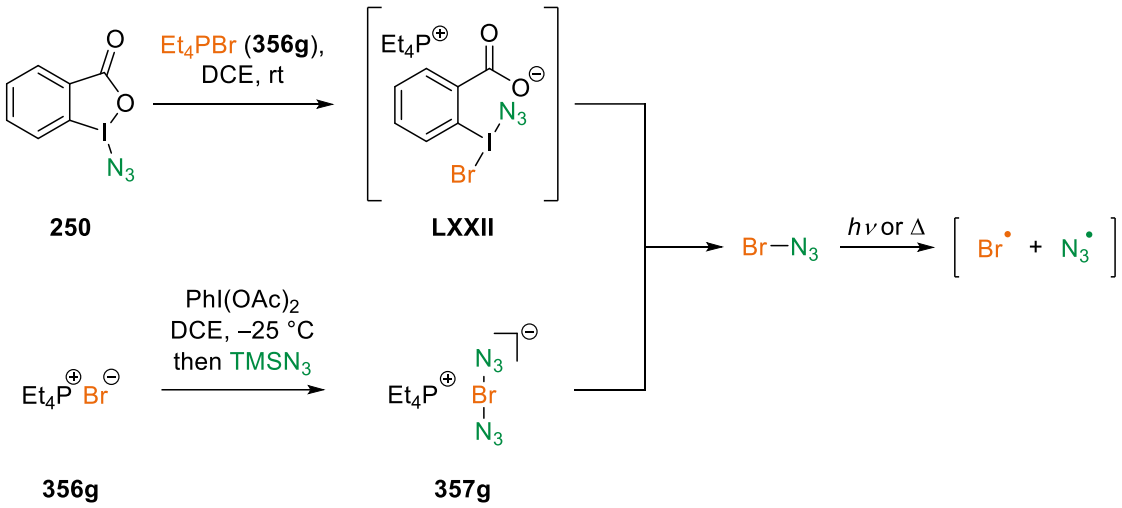
The concept of separating radical generation and chain termination in different compartments of the bi-phasic mixture offers the potential to be extended to further transformations. One starting point would be the investigation whether other oxidation-sensitive reagents that undergo addition reactions with alkyl radicals can be used instead of the aminoxyl radical. The challenge here is the requirement for the side reactions at the phase boundary to proceed more slowly than the phase transfer of the radical intermediate.

The research on polymer-bound iodate(I) complex **266** in close collaboration with KÖSEL led to the elucidation of the radical mechanisms behind the observed H-abstractions and the chemoselective oxidation of secondary alcohols. Additionally, a method for the azidooxygenation of alkenes was developed (Scheme 98). However, further optimization is still necessary to improve the synthetic potential of this transformation. Due to the polymeric nature of ion-exchange resin **266**, irradiation of the reaction mixtures proved to be problematic. However, exposure to a light source is essential to favor the radical reactivity over the ionic one. A comparison of the polymer-based method with the free salt form of the bis(azido)iodate(I) complex would therefore be interesting.



Scheme 98 Newly developed method for the azidooxygenation of alkenes using iodate(I) complex **266**.

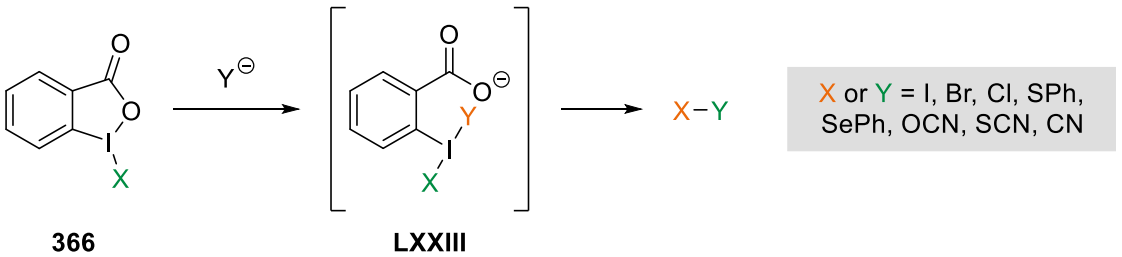
The studies on the *in situ* generation of bromine azide in organic solvents led to two fundamentally different methods (Scheme 99). One is based on a haloate(I) complex similar to the polymer-bound reagent **266**, while the second is utilized iodine(III) species **250**.



Scheme 99 Developed methods for *in situ* generation of bromine azide.

In close collaboration with GEORGE and TASER, both methods could be successfully applied to the selective oxidation of secondary alcohols and the bromoazidation of alkenes. The results varied greatly depending on the structure of the substrates. Especially for the chemoselective oxidation, the yields obtained were significantly lower than those reported for the polymer-bonded iodine azide reagent **266**.[209] It can be assumed that the reason for this is the low stability of bromine azide or the intermediate complexes. Especially at temperatures above 0 °C, a large amount of the active reagent decomposed almost immediately to form nitrogen and bromine. Increasing the equivalents turned out to be only partially beneficial, as recombination of the radicals became more likely at higher concentrations. The key thus lied in a slower and more controlled release of bromine azide at low temperatures.

The next step in continuing the project would be the extension of the method based on the benziodoxolone **250** to other pseudohalogens. For this purpose, either the iodine(III) reagent could be modified or other nucleophiles could be applied (Scheme 100).



Scheme 100 Possible extension of the method to other (pseudo)halides.

A similar approach could be followed for the haloate(I) complexes. Additionally, the influence of the counterions could be further investigated. Besides tetraalkylammonium and -phosphonium, trialkylsulfonium salts, for example, could be tested. These have been successfully applied by Kashyap's group for the generation of bis(acetoxy)iodate(I) and bis(azido)iodate(I) complexes.[178,213,220]

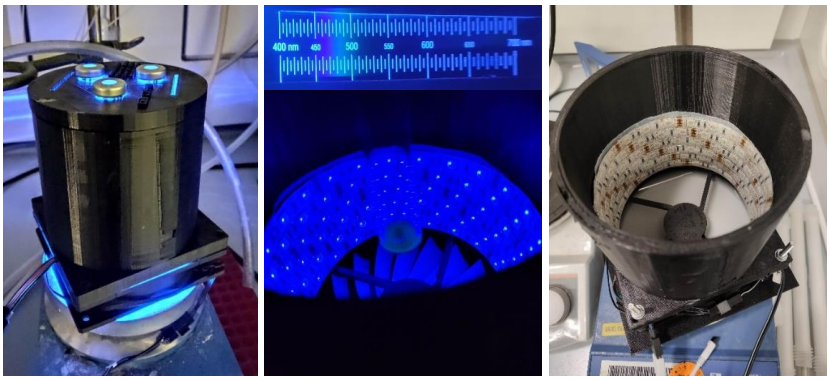
Experimental Section

E1 General Information

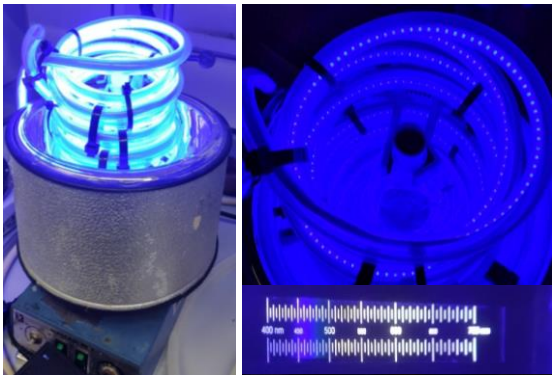
All reactions were carried out in dried glassware under argon or nitrogen. Anhydrous solvents (MeCN, CH_2Cl_2, Et_2O, PhMe) were obtained from a M. BRAUN MB solvent purification system or commercial solvents were used as supplied. Petroleum ether and dichloromethane were distilled before application and triethylamine was dried over KOH and distilled as well. Commercial reagents were used as supplied.

Reactions under **UV light irradiation** were performed using a 365 nm high intensity UV lamp (100 W) by ANALYTIKJENA, an ENDRESS+HAUSER Company.

Reactions under **blue LED light irradiation at room temperature** were carried out in a 3D printed photoreactor with a diameter of 115 mm. As light source a 5 m LED light strip with 60 LED/m (type 5050 RGB, 12 W/m) was used. A 120 mm PC fan was employed to cool the reactor to room temperature during the reaction. The color was set to blue (λ_{max} = 445 – 510 nm).



Reactions under **blue LED light irradiation at temperatures below room temperature** were carried out in a cryostat cooled *i*PrOH bath. A 5 m COB LED strip with 224 LED/m (10 W*m^{-1}, λ_{max} = 440 nm – 495 nm) was used as light source. The strip was partially submerged to ensure optimal irradiation conditions. The temperature of the cooling bath was controlled by an external thermometer.



^{1}H NMR spectra are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, sx = sextet, sp = septet, bs = broad singlet, m = multiplet), coupling constant (J) in hertz (Hz), integration and assignment. **^{13}C NMR** spectra are represented as follows: chemical shift, substitution (p = primary, s = secondary, t =tertiary, q = quaternary) and assignment. **^{19}F NMR** spectra are represented as follows: multiplicity (s = singlet, d = doublet,

t = triplet, q = quartet, qi = quintet, sx = sextet, sp = septet, bs = broad singlet, m = multiplet), coupling constant (J) in hertz (Hz), integration and assignment. **^{1}H NMR**, **^{13}C NMR** and **^{19}F NMR** spectra were recorded using a BRUKER Ultrashield 500 MHz with Avance-III HD console, a BRUKER Ascend 400 MHz with Avance-III console, a BRUKER Ascend 400 MHz with Avance-III HD console, a BRUKER Ultrashield 400 MHz with Avance-I console and a BRUKER Ascend 600 MHz with Avance Neo console.

High-resolution mass data (**HRMS**) was measured with a Micromass LCT with lockspray source. The injection proceeded in loop-mode with a HPLC system by WATERS (Alliance 2695). Alternatively, mass spectra were recorded with an Acquity-UPLC system by WATERS in combination with a Q-Tof Premier mass spectrometer by WATERS in lockspray mode. The ionization happened by electrospray ionization (ESI) or by chemical ionization at atmospheric pressure (APCI). The calculated and found mass are reported.

GC/MS analyses were carried out with an HP 6890 chromatograph with KAS 4, coupled to an HP 5973 quadrupole mass selective detector. Samples were analyzed on an OPTIMA 5 column (poly(5%-phenyl-95%-methylsiloxane), 30 m x 0.32 mm i.d. x film thickness 0.25 µm). Carrier gas, He; injector temp., 60 °C to 300 °C at 12 °C/min, splitless; temp. program: 50 °C (isothermal 1 min) to 300 °C, at 20 °C/min and held isothermal for 6 min at 300 °C; ion source: EI, ionization energy, 70 eV; electron mass spectra were acquired over the mass range of 40 – 500 amu.

X-ray structure analysis was performed using a BRUKER SMART X2S benchtop crystallographic system utilizing UCSF Chimera (version 1.14) software for visualisation.

Infrared spectra (ν_{max}, FTIR) were recorded in reciprocal centimeters (cm^{-1}) as thin films or compressed solids on a SHIMADZU FT-IR Affinity-1S spectrometer.

Melting points were determined on an SRS OptiMelt apparatus and are not corrected.

Specific Optical rotation values $[\alpha]^{T}_{D}$ were measured in a quartz cuvette on a polarimeter 341 by PERKINELMER at a wavelength of 589 nm (D) and given temperature T.

For **column chromatography**, silica gel (35-70 microns) was used. Alternatively, a BIOTAGE SP purification system was used. BIOTAGE silica cartridges were used as supplied.

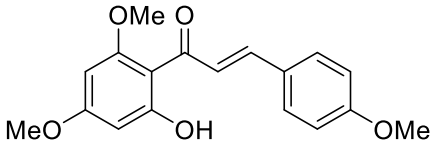
TLC was performed on aluminum-backed plates pre-coated (0.25 mm) with silica gel 60 F254 with a suitable solvent system and was visualized using UV fluorescence and/or developed with $KMnO_4$, DNPH, anisaldehyde or vanillin stain followed by brief heating.

Semi-preparative HPLC was performed using an Alliance 2695 HPLC-system by WATERS with a WATERS 996 diode array detector (λ = 200-350 nm) and a NUCLEODUR 100-5 C18 CN-RP column (5 µm, 250 mm, Ø 8 mm) by MACHERY NAGEL. Mass detection was conducted with a WATERS Quattro micro API mass spectrometer in positive ionization mode.

Chiral Preparative HPLC was performed using a GILSON HPLC-system (pump 331/332) with additional MERCK HITACHI Split-Pump (L-6200A, UV-Vis detector L-4250) and a PHENOMENEX Lux Cellulose-1 preparative column: (5 µm, 250, Ø 21.2 mm) Mass detection was conducted with a WATERS Micromass ZQ mass spectrometer in positive ionization mode. Operating conditions and retention times (t_R) are reported in the experimental details.

E2 Experimental Procedures – Topic A

(*E*)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (73)



73
$C_{18}H_{18}O_5$
MW: 314.34

Acetophenone **72** (500 mg, 2.55 mmol, 1.00 eq.) was added to a solution of NaOEt (1.04 g, 15.3 mmol, 6.00 eq.) in EtOH (8.8 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (341 µL, 2.80 mmol, 1.10 eq.) was added and the reaction mixture was stirred for 72 h. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and recrystallized from EtOH. The desired compound **73** was obtained as a yellow solid (533 mg, 1.70 mmol) in 67% yield.

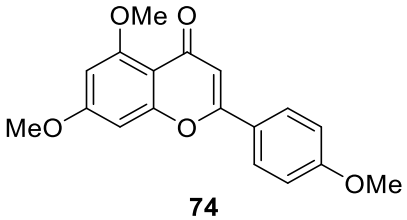
$\mathbf{R}_f$ = 0.27 (petroleum ether/EtOAc 7:2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.80 (d, J = 1.4 Hz, 2H, C(O)C*H*, C(O)CH=C*H*), 7.57 (d, J = 8.8 Hz 2H, 2x Ar*H*), 6.93 (d, J = 8.8 Hz, 2H, 2x Ar*H*), 6.11 (d, J = 2.3 Hz, 1H, Ar*H*), 5.96 (d, J = 2.3 Hz, 1H, Ar*H*), 3.92 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 192.7 (q, *C*=O), 168.5 (q, Ar*C*), 166.1 (q, Ar*C*), 162.6 (q, Ar*C*), 161.5 (q, Ar*C*), 142.6 (t, C(O)CH=*C*H), 130.2 (t, 2x Ar*C*H), 128.4 (q, Ar*C*), 125.2 (t, C(O)*C*H), 114.5 (t, 2x Ar*C*H), 106.4 (q, Ar*C*), 93.9 (t, Ar*C*H), 91.3 (t, Ar*C*H), 55.9 (p, O*C*H$_3$), 55.7 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$).

The analytical data are consistent with those reported in the literature.[221]

5,7-Dimethoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (74)



74
$C_{18}H_{16}O_5$
MW: 312.32

A solution of 4',5,7-trimethoxychalcone (**73**) (500 mg, 1.62 mmol, 1.00 eq.) in DMSO (1.55 mL) was treated with a catalytic amount of iodine (29 mg, 114 µmol, 0.07 eq.) and stirred at 140 °C for 2 h. After completion of the reaction, the mixture was poured into a flask containing ice-cold H_2O and $Na_2S_2O_3$ solution (aq., sat.). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **74** was obtained as a yellow solid (471 mg, 1.51 mmol) in 93% yield.

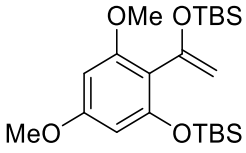
$\mathbf{R}_f$ = 0.34 (CH_2Cl_2/acetone 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.81 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 6.99 (d, J = 8.9 Hz 2H, 2x Ar*H*), 6.58 (s, 1H, C=C*H*C(O)), 6.55 (d, J = 2.2 Hz, 1H, Ar*H*), 6.36 (d, J = 2.2 Hz, 1H, Ar*H*), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 177.8 (q, *C*=O). 164.0 (q, Ar*C*), 162.1 (q, *C*=CHC(O)), 161.0 (q, Ar*C*), 160.8 (q, Ar*C*), 159.9 (q, Ar*C*), 127.7 (t, 2x Ar*C*H), 123.9 (q, Ar*C*), 114.5 (t, 2x Ar*C*H), 109.3 (q, Ar*C*), 107.8 (t, C=*C*HC(O)), 96.2 (s t, Ar*C*H), 92.9 (t, Ar*C*H), 56.6 (p, O*C*H_3), 55.9 (p, O*C*H_3), 55.6 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[222]

tert-Butyl((1-(2-((*tert*-butyldimethylsilyl)oxy)-4,6-dimethoxyphenyl)vinyl)oxy)dimethylsilane (E1)

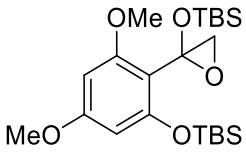


E1
$C_{22}H_{40}O_4Si_2$
MW: 424.73

A solution of 4-benzyloxy-2-hydroxy-6-methoxyacetophenone (**72**) (600 mg, 3.06 mmol, 1.00 eq.) in CH_2Cl_2 (7.66 mL) was cooled to 0 °C, treated with triethylamine (1.27 mL, 9.17 mmol, 3.00 eq.) and TBSOTf (1.93 mL, 8.41 mmol, 2.75 eq.) and stirred at 0 °C for 30 min. The reaction was terminated by the addition of $NaHCO_3$ solution (aq., sat.) and was allowed to warm to rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yielding two-phasic mixture of product and triethylammonium triflate was diluted with Et_2O and NH_4Cl solution (aq., sat.), followed by phase seperation. The aqueous phase was extracted with Et_2O (100 mL, 3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The TBS enol ether **E1** was obtained as a clear colorless oil (1.19 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.69 (petroleum ether/EtOAc 5:1).

tert-Butyl((2-(2-((*tert*-butyldimethylsilyl)oxy)-4,6-dimethoxyphenyl)oxiran-2-yl)oxy)dimethylsilane (E2)

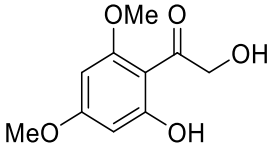


E2
$C_{22}H_{40}O_5Si_2$
MW: 440.73

TBS enol ether **E1** (1.19 g, 2.82 mmol, 1.00 eq.) was added to a suspension of *m*CPBA (77 wt%, 1.10 g, 4.89 mmol, 1.60 eq.) and $NaHCO_3$ (640 mg, 7.65 mmol, 2.50 eq.) in CH_2Cl_2 (15.3 mL) at 0 °C. The resulting mixture was allowed to warm to rt and was stirred for 2 h. Then, it was diluted with CH_2Cl_2, washed with $NaHCO_3$ (aq., sat.) and H_2O, dried over $MgSO_4$ and filtered. After concentration under reduced pressure, the epoxide **E2** was obtained as a colorless, clear oil (1.16 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.53 (petroleum ether/EtOAc 5:1).

2-Hydroxy-1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (75)



75
$C_{10}H_{12}O_5$
MW: 212.20

A solution of crude epoxide **E2** (1.16 g, 2.63 mmol, 1.00 eq.) in THF (15.3 mL) and H_2O (1.50 mL) was treated with *p*TsOH·H_2O (50.0 mg, 26.3 µmol, 10 mol%) and heated under refluxing conditions for 12 h. Subsequently, the mixture was allowed to cool to rt and partitioned between EtOAc and $NaHCO_3$ solution (aq., sat.). After separation of the phases, the aqueous phase was extracted using EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification by column chromatography (petroleum ether/EtOAc 5:1 → 2:1) the desired *α*-hydroxy ketone **75** was obtained as a yellow-orange solid (450 mg, 2.10 mmol) in 69% yield over three steps.

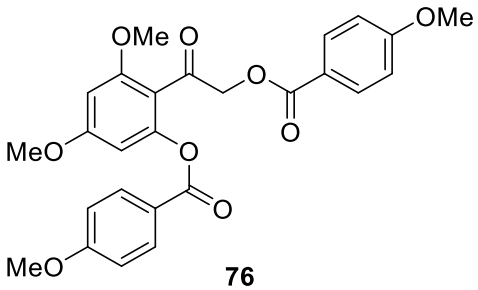
$\mathbf{R}_f$ = 0.23 (petroleum ether/EtOAc 5:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.22 (s, 1H, O*H*), 6.10 (d, J = 2.3 Hz, 1H, Ar*H*), 5.93 (d, J = 2.3 Hz, 1H, Ar*H*), 4.71 (d, J = 4.7 Hz, 2H, CH_2OH), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 201.9 (q, *C*=O), 167.3 (q, Ar*C*), 167.1 (q, Ar*C*), 163.32 (q, Ar*C*), 93.8 (t, Ar*C*H), 91.0 (t, Ar*C*H), 68.9 (s, *C*H_2OH), 55.73 (p, O*C*H_3), 55.71 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[72]

3,5-Dimethoxy-2-(2-((4-methoxybenzoyl)oxy)acetyl)phenyl 4-methoxybenzoate (76)

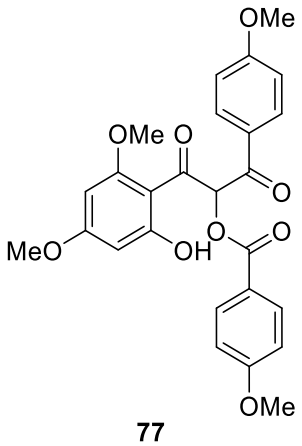


76
$C_{26}H_{24}O_9$
MW: 480.47

A solution of the *α*-hydroxy ketone **75** (450 mg, 2.10 mmol, 1.00 eq.) in CH_2Cl_2 (21.0 mL) was treated with *p*-anisic acid (960 mg, 6.29 mmol, 3.00 eq.), 4-DMAP (87.0 mg, 712 µmol, 34 mol%) and EDC·HCl (1.81 g, 9.44 mmol, 4.50 eq.). The mixture was stirred at rt for 8 h and then terminated by the addition of H_2O. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired bisbenzoate **76** was obtained as a yellow foam (640 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.31 (petroleum ether/EtOAc 3:1).

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-1,3-dioxopropan-2-yl 4-methoxybenzoate (77)

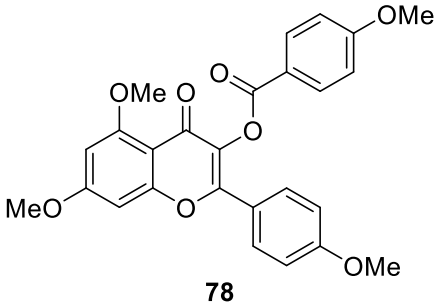


77
$C_{26}H_{24}O_9$
MW: 480.47

A solution of crude bisbenzoate **76** (570 mg, 1.18 mmol, 1.00 eq.) in THF (35.0 mL) was cooled to –20 °C and treated with LiHMDS (1.00 M in THF, 3.64 mL, 3.64 mmol, 3.08 eq.). The mixture was stirred at –20 °C for 2 h. Then, the reaction was terminated by the addition of $NaHCO_3$ solution (aq., sat.) and was allowed to warm to rt. After separation of the phases, the aqueous phase was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired phenol **77** was obtained as a yellow foam (550 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.19 (petroleum ether/EtOAc 3:1).

5,7-Dimethoxy-2-(4-methoxyphenyl)-4-oxo-4*H*-chromen-3-yl 4-methoxybenzoate (78)



78
$C_{26}H_{22}O_8$
MW: 462.45

A suspension of crude phenol **77** (550 mg, 1.15 mmol, 1.00 eq.) in AcOH (15.0 mL) was treated with H_2SO_4 (96 wt%, 300 µL, 5.45 mmol, 4.75 eq.) and stirred at rt for 20 h. The reaction mixture was poured into ice-cold H_2O and stirred for 15 min. Thereby, a precipitate was formed. The mixture was filtered on a BÜCHNER funnel and the precipitate was washed with H_2O. The wet solid was suspended in a minimal amount of ethanol and heated to reflux for 1 h. The mixture was allowed to cool to rt, filtered on a BÜCHNER funnel and washed with a small amount of cold ethanol. The solid was dried under reduced pressure to constant weight to give the desired 3-benzyloxyflavonate **78** as pale-yellow solid (390 mg, 844 µmol) in 40% yield over three steps.

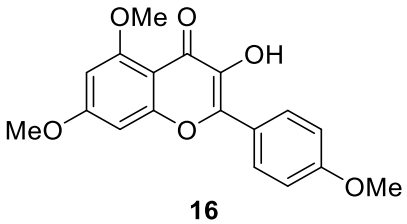
$\mathbf{R}_f$ = 0.26 (petroleum ether/EtOAc 1:2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.16 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 7.88 (d, J = 9.0 Hz, 2H, 2x Ar*H*), 6.98 – 6.93 (m, 4H, 4x Ar*H*), 6.55 (d, J = 2.2 Hz, 1H, Ar*H*), 6.36 (d, J = 2.2 Hz, 1H, Ar*H*), 5.16 (s, 2H, CH_2), 3.91 (s, 6H, 2x OCH_3), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.9 (q, *C*=O), 164.3 (q, Ar*C*), 164.0 (q, Ar*C*), 163.9 (q, O*C*=O), 161.6 (q, Ar*C*), 161.4 (q, Ar*C*), 159.3 (q, Ar*C*), 153.4 (q, *C*=C-C=O), 134.0 (q, O=C-*C*=C), 132.8 (t, 2x Ar*C*), 129.8 (t, 2x Ar*C*), 122.5 (q, Ar*C*), 121.6 (q, Ar*C*), 114.2 (t, 2x Ar*C*), 113.8 (t, 2x Ar*C*), 109.0 (q, Ar*C*), 96.1 (t, Ar*C*H), 92.6 (t, Ar*C*H), 56.4 (s, O*C*H$_3$), 56.4 (p, O*C*H$_3$), 55.6 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{22}O_8Na$ $[M+Na]^+$ 485.1212, found 485.1211.

3-Hydroxy-5,7-dimethoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (16)



16

$C_{18}H_{16}O_6$

MW: 328.32

Method A from flavone 74

Flavone **74** (200 mg, 640 µmol, 1.00 eq.) and Na_2CO_3/$NaHCO_3$ buffer solution (pH = 9, 48.0 mL) were added to a mixture of acetone (14.3 mL) and CH_2Cl_2 (19.0 mL). A solution of Oxone® (2.85 g, 9.29 mmol, 14.5 eq.) in H_2O (33.0 mL) was added and the biphasic mixture was stirred for 24 hours at rt, keeping the pH at 9. Subsequently, a second portion of acetone (14.0 mL) and Oxone® (2.85 g, 9.29 mmol, 14.5 eq.) was added. After stirring for additional 2 h, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with $Na_2S_2O_3$ solution (aq., sat.) and NaCl solution (aq., sat.), dried over $MgSO_4$ and filtered. To the filtrate was added a catalytic amount of *p*TsOH and stirred for 1 h. Then, the solvent was removed under reduced pressure to afford a yellow solid (53 mg) which could not be completely purified neither by recrystallization from aqueous EtOH (*v*/*v* 80%) nor by column chromatography. Analysis of the crude ^{1}H NMR spectrum revealed a mixture of product and starting material in a ratio of 4:1, corresponding to a yield of 20 % for the flavonol **16** (42.4 mg, 129 µmol).

Method B from flavonol ester 78

A suspension of flavonol ester **78** (388 mg, 839 µmol, 1.00 eq.) in EtOH (4.70 mL) was treated with NaOH solution (1.00 M in H_2O, 1.13 mL, 1.13 mmol, 1.35 eq.). The yellowish suspension was stirred at 80 °C for 5 h. The reaction mixture was allowed to cool to rt and was neutralized with HCl (1.00 M in H_2O, 2.26 mL, 2.26 mmol, 2.00 eq.). The resulting suspension was filtered on a BÜCHNER funnel and the precipitate was washed with a small amount of cold ethanol. The solid dissolved in CH_2Cl_2 and washed with K_2CO_3 solution (10% in H_2O). After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the desired flavonol **16** as a pale-yellow solid (268 mg, 816 µmol) in 97% yield.

Method C from chalcone 73

To a suspension of chalcone **73** (565 mg, 1.80 mmol, 1.00 eq.) in MeOH (15.5 mL), NaOH (3.00 M, aq., 2.32 mL, 6.96 mmol, 3.87 eq.) was added and cooled to 0 °C. H_2O_2 (30 wt% in H_2O, 586 µL, 5.75 mmol, 3.20 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 20 h. HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate and the suspension was extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (petroleum ether/EtOAc 1:2) and recrystallization from aqueous EtOH (*v/v* 80%) to give the desired flavonol **16** as a pale-yellow solid (26.3 mg, 80.1 µmol) in 4% yield.

Method D from *ortho*-hydroxy acetophenone 72

An Erlenmeyer flask was charged with a relatively large stirring bar, H_2O (10.0 mL) and pyrrolidine (494 µL, 6.01 mmol, 10.0 eq.). At maximum stirring speed, 4-methoxybenzaldehyde (76.8 µL, 631 µmol, 1.05 eq.) was added. After stirring for 5 min at rt, the finely grounded acetophenone **72** (118 mg, 601 µmol, 1.00 eq.) was added in portions. The resulting mixture was stirred at 50 °C for 24 h and then allowed to cool to rt, poured into ice-cold H_2O and acidified to pH = 4 with HCl (37 wt% in H_2O). The resulting precipitate was filtered and washed with H_2O. The crude product was recrystallized from aqueous EtOH (*v/v* 80%) to afford the desired flavonol **16** as a pale-yellow solid (100 mg, 305 µmol) in 51% yield.

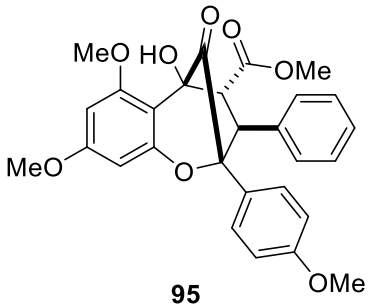
$\mathbf{R}_f$ = 0.60 (CH_2Cl_2/EtOAc 7:2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.17 (d, J = 8.8 Hz, 2H, 2x Ar*H*), 7.36 (bs, 1H, O*H*), 7.02 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 6.54 (d, J = 1.6 Hz, 1H, Ar*H*), 6.34 (d, J = 1.4 Hz, 1H, Ar*H*), 3.97 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.1 (q, *C*=O), 164.4 (q, Ar*C*), 160.8 (q, Ar*C*), 160.7 (q, Ar*C*), 159.0 (q, Ar*C*), 142.4 (q, *C*=COH), 137.6 (q, *C*OH), 129.0 (t, 2x Ar*C*), 123.7 (q. Ar*C*), 114.1 (t, 2x Ar*C*), 106.4 (q, Ar*C*), 95.8 (t, Ar*C*H), 92.5 (t, Ar*C*H), 56.5 (p, O*C*H$_3$), 55.9 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$).

The analytical data are consistent with those reported in the literature.[88]

(±)-(3*S*,4*S*,5*R*)-5-hydroxy-6,8-dimethoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (95)



95

$C_{28}H_{26}O_8$

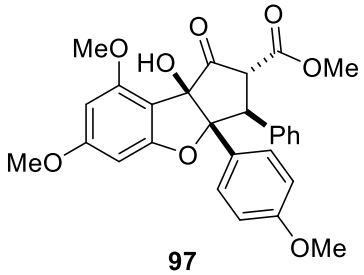
MW: 490.51

Methyl cinnamate (814 mg, 5.02 mmol, 14.2 eq.) was added to a solution of flavonol **16** (116 mg, 353 µmol, 1.00 eq.) in dry chloroform (6.93 mL) and freshly distilled 2,2,2-trifluoroethanol (2.94 mL).

The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure and the remaining amount of methyl cinnamate was removed by column chromatography (petroleum ether/EtOAc 3:1 ⟶ 0:1). Product **95** was obtained as a mixture of isomers as a yellowish foam (140 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.22 – 0.51 (petroleum ether/EtOAc 2:3).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-8b-hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (97)



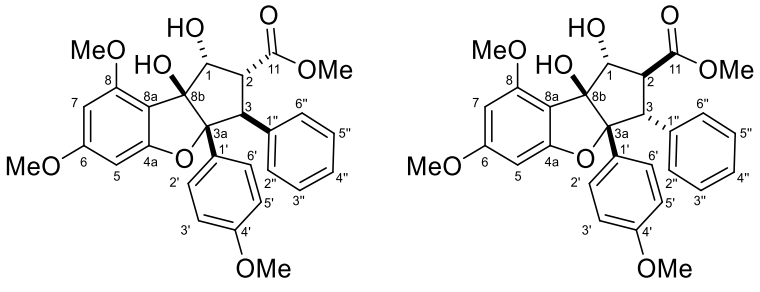
97

$C_{28}H_{26}O_8$
MW: 490.51

Cycloadduct **95** (140 mg, 286 µmol, 1.00 eq.) was dissolved in MeOH (7.92 mL). Then, NaOMe solution (25 wt% in MeOH, 164 µL, 801 µmol, 2.80 eq.) was added and the mixture was heated under refluxing conditions for 40 min. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The desired product **97** was obtained as a mixture of isomers as a yellow foam (134 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.32 (petroleum ether/EtOAc 2:3).

(±)-Methyl (1R,2R,3S,3aR,8bS)-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxylate ((±)-endo-59)



(±)-*endo*-59 **(±)-*exo*-59**

$C_{28}H_{28}O_8$
MW: 492.52

A mixture of $(CH_3)_4N(OAc)_3BH$ (460 mg, 1.75 mmol, 6.42 eq.) and freshly distilled AcOH (162 µL, 2.83 mmol, 10.4 eq.) in MeCN (7.07 mL) was stirred for 5 min at rt. Then, a solution of keto ester **97** (134 mg, 272 µmol, 1.00 eq.) in MeCN (4.69 mL) was added. The mixture was protected from light and

stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (petroleum ether/EtOAc 3:2) was then performed to obtain the racemic *endo*-product **(±)-*endo*-59** as a colorless foam (76.9 mg, 156 µmol) in 44% yield over 3 steps. In addition, the racemic *exo*-product **(±)-*exo*-59** was obtained as a pale-yellow foam (16.9 mg, 34.3 µmol) in 10% yield over 3 steps.

(±)-*endo*-59:

R_f = 0.34 (petroleum ether/EtOAc 2:3).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.06 – 6.96 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.87 (d, $\mathcal{J}$ = 7.4 Hz, 2H, *H*-2'', *H*-6''), 6.59 (d, $\mathcal{J}$ = 8.6 Hz, 2H, *H*-3', *H*-5'), 6.28 (bs, 1H, *H*-5), 6.11 (bs, 1H, *H*-7), 5.07 (s, 1H, O*H*-8b), 5.01 (d, $\mathcal{J}$ = 4.4 Hz, 1H, O*H*-1), 4.69 (t, $\mathcal{J}$ = 4.9 Hz, 1H, *H*-1), 4.14 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 3.91 (dd, $\mathcal{J}$ = 14.0, 5.5 Hz, 1H, *H*-2), 3.78 (p, H_3CO-6), 3.73 (p, H_3CO-8), 3.60 (s, 3H, H_3CO-4'), 3.54 (s, 3H, H_3CO-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.3 (q, *C*-11), 162.7 (q, *C*-6), 160.4 (q, *C*-4a), 157.8 (q, *C*-8), 157.5 (q, *C*-4'), 138.3 (q, *C*-1''), 128.7 (t, C-2', C-6'), 128.5 (q. *C*-1'), 127.7 (t, *C*-3'', *C*-5''), 127.4 (t, C-2'', C-6''), 125.8 (t, C-4''), 111.8 (t, *C*-3', *C*-5'), 108.3 (q, *C*-8a), 101.3 (q, *C*-3a), 93.2 (q, *C*-8b), 91.8 (t, *C*-7), 88.4 (t, *C*-5), 78.9 (t, *C*-1), 55.5 (p, H_3CO-6), 55.3 (p, H_3CO-8), 54.7 (p, H_3CO-4'), 54.6 (t, *C*-3), 51.3 (p, H_3CO-11), 50.6 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{28}H_{28}O_8Na$ $[M+Na]^+$ 515.1682, found 515.1681.

The analytical data are consistent with those reported in the literature.[70]

(±)-*exo*-59:

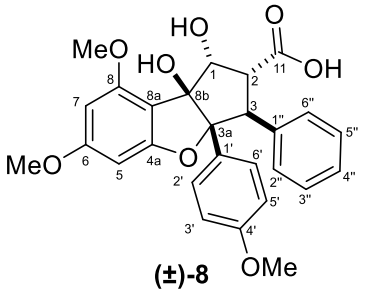
R_f = 0.21 (petroleum ether/EtOAc 2:3).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.23 (d, $\mathcal{J}$ = 8.8 Hz, 2H, *H*-2', *H*-6'), 7.18 – 7.13 (m, 3H, *H*-3'', *H*-4'', *H*-5''), 6.93 – 6.91 (m, 2H, *H*-2'', *H*-6''), 6.87 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-3', *H*-5'), 6.16 (d, $\mathcal{J}$ = 1.9 Hz, 1H, *H*-5), 6.11 (d, $\mathcal{J}$ = 1.9 Hz, 1H, *H*-7), 5.18 (s, 1H, O*H*-8b), 5.06 (d, $\mathcal{J}$ = 4.9 Hz, 1H, O*H*-1), 4.51 (dd, $\mathcal{J}$ = 10.4, 5.0 Hz, 1H, *H*-1), 3.81 (d, $\mathcal{J}$ = 12.8 Hz, 1H, *H*-3), 3.75 (s, 3H, H_3CO-6), 3.72 (s, 3H, H_3CO-4'), 3.69 (s, 3H, H_3CO-8), 3.47 (s, 3H, H_3CO-11), 2.98 (dd, $\mathcal{J}$ = 12.8, 10.5 Hz, 1H, *H*-2).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 173.1 (q, *C*-11), 162.5 (q, *C*-6), 161.0 (q, *C*-4a), 159.0 (q, *C*-8), 158.2 (q, *C*-4'), 135.6 (q, *C*-1''), 130.1 (t, *C*-4''), 128.8 (t, *C*-2', *C*-6'), 128.3 (t, *C*-2'', *C*-6''), 127.7 (t, C-3'', C-5''), 126.8 (q, *C*-1'), 112.7 (t, *C*-3', *C*-5'), 106.2 (q, *C*-8a), 99.0 (q, *C*-3a), 92.3 (t, *C*-5), 90.6 (q, *C*-8b), 87.7 (t, *C*-7), 83.5 (t, *C*-1), 55.5 (p, H_3CO-6), 55.4 (p, H_3CO-8), 55.0 (p, H_3CO-4'), 53.7 (t, *C*-3), 51.6 (p, H_3CO-11), 50.8 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[89]

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid ((±)-8)



(±)-8

$C_{27}H_{26}O_8$

MW: 478.50

A solution of methyl ester **(±)-*endo*-59** (54.0 mg, 110 µmol, 1.00 eq.) and lithium hydroxide (2.00 M in H_2O, 280 µL, 559 µmol, 5.10 eq.) in MeOH (1.71 mL) was heated at 50 °C for 200 min. The solution was allowed to cool to rt, acidified with HCl (1.00 M in H_2O) to pH 1-2 and diluted with CH_2Cl_2 (5.00 mL) and H_2O (5.00 mL). The organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2x 5.00 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the rocagloic acid (**(±)-8**) as a yellowish solid (52.0 mg, 109 µmol) in 99% yield.

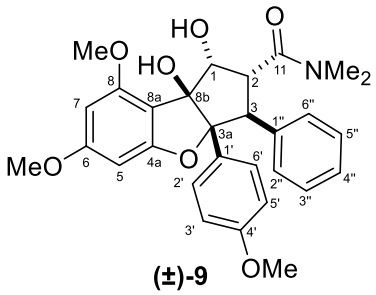
$\mathbf{R}_f$ = 0.25 (EtOAc).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.05 – 6.93 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.81 (d, $\mathcal{J}$ = 7.2 Hz, 2H, *H*-2'', *H*-6''), 6.61 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 6.31 (d, $\mathcal{J}$ = 2.0 Hz, 1H, *H*-5), 6.14 (d, $\mathcal{J}$ = 2.0 Hz, 1H, *H*-7), 5.03 (s, 1H, O*H*-8b), 4.80 (dd, $\mathcal{J}$ = 6.5, 3.7 Hz, 1H, *H*-1), 4.58 (d, $\mathcal{J}$ = 3.6 Hz, 1H, O*H*-1), 4.21 (d, $\mathcal{J}$ = 13.5 Hz, 1H, *H*-3), 4.01 (dd, $\mathcal{J}$ = 13.4, 6.6 Hz, 1H, *H*-2), 3.79 (p, H_3CO-8), 3.76 (p, H_3CO-6), 3.61 (s, 3H, H_3CO-4'), 3.23 (s, 3H, NCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 174.8 (q, *C*-11), 164.2 (q, *C*-6), 161.0 (q, *C*-4a), 158.9 (q, *C*-4'), 157.1 (q, *C*-8), 136.9 (q, *C*-1''), 129.1 (t, C-2', C-6'), 128.0 (t, *C*-3'', *C*-5''), 127.9 (t, C-2'', C-6''), 126.7 (t, C-4''), 126.5 (q. *C*-1'), 112.9 (t, *C*-3', *C*-5'), 107.6 (q, *C*-8a), 102.0 (q, *C*-3a), 93.8 (q, *C*-8b), 92.8 (t, *C*-7), 89.6 (t, *C*-5), 79.5 (t, *C*-1), 55.9 (p, H_3CO-8), 55.8 (p, H_3CO-6), 55.2 (p, H_3CO-4'), 55.1 (t, *C*-3), 50.4 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[223]

(±)-(1R,2R,3S,3aR,8bS)-1,8b-Dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide ((±)-rocaglamide, (±)-9)



(±)-9

$C_{29}H_{31}NO_7$

MW: 505.57

To a solution of rocagloic acid (**(±)-8**) (25.0 mg, 52.2 µmol, 1.00 eq.) in DMF (1.52 mL) was added dimethylamine hydrochloride (5.1 mg, 62.7 µmol, 1.20 eq.) and 4-DMAP (7.7 mg, 62.7 µmol, 1.20 eq.). After cooling the reaction mixture to 0 °C, EDC·HCl (12.0 mg, 62.7 µmol, 1.20 eq.) was added in portions over 5 min. After stirring for 30 min, triethylamine (8.7 µL, 62.7 µmol, 1.20 eq.) was added and the cooling bath was removed. When the starting material was fully consumed (13 h), HCl (1.00 M in H_2O) was added and the mixture was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (CH_2Cl_2/MeOH 95:5) to afford (±)-rocaglamide (**(±)-9)** as a colorless solid (2.4 mg, 4.75 µmol) in 9% yield.

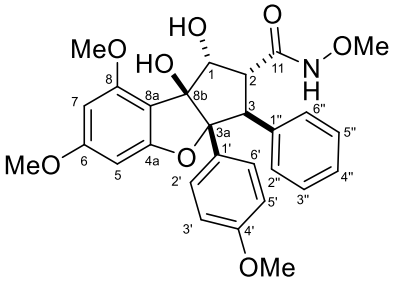
$\mathbf{R}_f$ = 0.45 (CH_2Cl_2/MeOH 95:5).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.05 – 6.93 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.81 (d, $\mathcal{J}$ = 7.2 Hz, 2H, *H*-2'', *H*-6''), 6.61 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 6.31 (d, $\mathcal{J}$ = 2.0 Hz, 1H, *H*-5), 6.14 (d, $\mathcal{J}$ = 2.0 Hz, 1H, *H*-7), 5.03 (s, 1H, O*H*-8b), 4.80 (dd, $\mathcal{J}$ = 6.5, 3.7 Hz, 1H, *H*-1), 4.58 (d, $\mathcal{J}$ = 3.6 Hz, 1H, O*H*-1), 4.21 (d, $\mathcal{J}$ = 13.5 Hz, 1H, *H*-3), 4.01 (dd, $\mathcal{J}$ = 13.4, 6.6 Hz, 1H, *H*-2), 3.79 (p, H_3CO-8), 3.76 (p, H_3CO-6), 3.61 (s, 3H, H_3CO-4'), 3.23 (s, 3H, NCH_3), 2.74 (s, 3H, NCH_3).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 168.5 (q, *C*-11), 162.7 (q, *C*-6), 160.3 (q, *C*-4a), 157.6 (q, *C*-8), 157.4 (q, *C*-4'), 139.2 (q, *C*-1''), 128.8 (t, C-2', C-6'), 128.6 (q. *C*-1'), 127.7 (t, *C*-3'', *C*-5''), 127.2 (t, C-2'', C-6''), 125.5 (t, C-4''), 111.9 (t, *C*-3', *C*-5'), 108.9 (q, *C*-8a), 101.1 (q, *C*-3a), 93.5 (q, *C*-8b), 91.9 (t, *C*-7), 88.8 (t, *C*-5), 78.2 (t, *C*-1), 55.5 (p, H_3CO-8), 55.4 (p, H_3CO-6), 55.3 (t, *C*-3), 54.7 (p, H_3CO-4'), 47.8 (t, *C*-2), 36.4 (p, NCH_3), 35.1 (p, N*C*H_3).

The analytical data are consistent with those reported in the literature.[224]

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-*N*,6,8-trimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-CR-31-B, (±)-13)



(±)-13
$C_{28}H_{29}NO_8$
MW: 507.54

To a solution of rocagloic acid (**(±)-8**) (25.0 mg, 52.2 µmol, 1.00 eq.) in CH_2Cl_2 (3.71 mL) EDC·HCl (15.0 mg, 78.4 µmol, 1.50 eq.), HOBt·H_2O (10.7 mg, 67.9 µmol, 1.30 eq.), methoxylamine hydrochloride (21.8 mg, 261 µmol, 5.00 eq.) and triethylamine (36.2 µL, 261 µmol, 5.00 eq.) were added. The mixture was then stirred at rt for 12 h. Subsequently, the reaction was terminated by the addition of HCl (1.00 M in H_2O), extracted with CH_2Cl_2 (3x), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (CH_2Cl_2/MeOH 95:5). (±)-CR-31-B (**(±)-13**) was obtained as a colorless solid (11.8 mg, 23.2 µmol) in 44% yield.

$\mathbf{R}_f$ = 0.48 (CH_2Cl_2/MeOH 9:1).

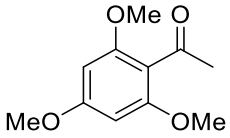
^{1}H-NMR (DMSO-d_6, 500 MHz): δ [ppm] 11.15 (s, 1H, N*H*), 7.06 – 6.96 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.89 (d, $\mathcal{J}$ = 7.5 Hz, 2H, *H*-2'', *H*-6''), 6.60 (d, $\mathcal{J}$ = 8.8 Hz, 2H, *H*-3', *H*-5'), 6.28 (d, $\mathcal{J}$ = 1.7 Hz, 1H, *H*-5), 6.12 (d, $\mathcal{J}$ = 1.7 Hz, 1H, *H*-7), 5.01 (s, 1H, O*H*-8b), 4.65 (d, $\mathcal{J}$ = 3.8 Hz, 1H, O*H*-1), 4.57- 4.55 (m, 1H, *H*-1), 4.18 (d, $\mathcal{J}$ = 14.1 Hz, 1H, *H*-3), 3.78 (p, H_3CO-8), 3.74 (p, H_3CO-6), 3.61 (s, 3H, CH_3O-4'), 3.58 (dd, $\mathcal{J}$ = 14.2, 5.6 Hz, 1H, *H*-2), 3.49 (s, 3H, NHOCH_3).

^{13}C-NMR (DMSO-d_6, 125 MHz): δ [ppm] 166.4 (q, *C*-11), 162.7 (q, *C*-6), 160.5 (q, *C*-4a), 157.8 (q, *C*-8), 157.5 (q, *C*-4'), 138.3 (q, *C*-1''), 128.7 (t, C-2', C-6'), 128.6 (q. *C*-1'), 127.8 (t, *C*-3'', *C*-5''), 127.3 (t, C-2'', C-6''), 125.8 (t, C-4''), 111.8 (t, *C*-3', *C*-5'), 108.5 (q, *C*-8a), 101.1 (q, *C*-3a), 93.4 (q, *C*-8b), 91.8 (t, *C*-7), 88.5 (t, *C*-5), 79.0 (t, *C*-1), 63.1 (p, NHO*C*H_3), 55.5 (p, H_3CO-8), 55.4 (p, H_3CO-6), 54.8 (p, H_3CO-4'), 54.4 (t, *C*-3), 48.0 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{28}H_{29}NO_8Na$ $[M+Na]^+$ 530.1791, found 530.1792.

The analytical data are consistent with those reported in the literature.[63]

1-(2,4,6-Trimethoxyphenyl)ethan-1-one (104)



104
$C_{11}H_{14}O_4$
MW: 210.23

An oven-dried vial was charged with 1,3,5-trimethoxybenzene (**100**) (20.0 g, 119 mmol, 1.00 eq.) and TFA (130 mL). The green solution was cooled to 0 °C and acetic anhydride (22.5 mL, 238 mmol, 2.00 eq.) was added dropwise over a period of 10 min. During this process, the color of the reaction mixture changed to brown. After removing the cooling bath and stirring for 5 min at rt, the reaction mixture was cooled to 0 °C and terminated by the addition of ice-cold H_2O (500 mL). Then, the solution was neutralized with solid NaOH under cooling. The product, which precipitates as a colorless, crystalline solid, was filtered off, washed with H_2O and dried under reduced pressure at 70 °C. 1-(2,4,6-Trimethoxyphenyl)ethan-1-one (**104**) was obtained as a colorless solid (24.2 g, 115 mmol) in 97% yield.

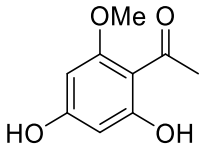
$\mathbf{R}_f$ = 0.31 (petroleum ether/MTBE 2:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.10 (s, 2H, 2x Ar*H*), 3.82 (s, 3H, OCH_3), 3.79 (s, 6H, 2x OCH_3), 2.46 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 201.9 (q, *C*=O), 162.5 (q, Ar*C*), 158.5 (q, 2x Ar*C*), 90.7 (t, 2x Ar*C*), 56.0 (p, 2x O*C*H_3), 55.6 (p, O*C*H_3), 32.7 (p, *C*H_3).

The analytical data are consistent with those reported in the literature.[225]

1-(2,4-Dihydroxy-6-methoxyphenyl)ethan-1-one (105)



105
$C_9H_{10}O_4$
MW: 182.18

A mixture of 1-(2,4,6-trimethoxyphenyl)ethan-1-one (**104**) (24.2 g, 115 mmol, 1.00 eq.), anhydrous $AlCl_3$ (30.7 g, 231 mmol, 2.00 eq.) and chlorobenzene (175 mL) was heated under refluxing conditions for 20 min. Then, the reaction mixture was cooled to 0 °C before HCl (10 wt%, aq.) was added. The resulting precipitate was filtered off and dissolved in EtOAc. The organic phase was extracted using NaOH (10 wt%, aq., 3x). The combined aqueous layers were brought to a pH of 11 with AcOH and extracted with EtOAc (6x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to obtain the desired product **105** as a pale-yellow solid (9.17 g, 50.4 mmol) in 44% yield.

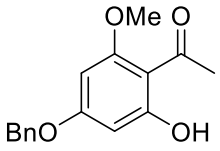
$\mathbf{R}_f$ = 0.33 (CH_2Cl_2/MeOH 95:5).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 13.81 (s, 1H, O*H*), 10.4 (s, 1H, O*H*), 5.97 (d, $\mathcal{J}$ = 2.0 Hz, 1H, Ar*H*), 5.86 (d, $\mathcal{J}$ = 2.2 Hz, 1H, Ar*H*), 3.82 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 202.3 (q, *C*=O), 166.3 (q, Ar*C*), 165.1 (q, Ar*C*), 163.3 (q, Ar*C*), 104.6 (q, Ar*C)*, 95.6 (t, Ar*C*H), 91.3 (t, Ar*C*H), 55.8 (p, O*C*H$_3$), 32.6 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[226]

1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)ethan-1-one (101)



101
$C_{16}H_{16}O_4$
MW: 272.30

1-(2,4-Dihydroxy-6-methoxyphenyl)ethan-1-one (**105**) (11.1 g, 60.9 mmol, 1.00 eq.) was dissolved in dry acetone (250 mL). After adding K_2CO_3 (10.1 g, 73.1 mmol, 1.20 eq.) and benzyl bromide (7.24 mL, 60.9 mmol, 1.00 eq.), the suspension was heated under refluxing conditions for 16 h. Then, the mixture was filtered and the solvent was evaporated. The crude product was purified by column chromatography (petroleum ether/EtOAc 6:1). 1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)ethan-1-one (**101**) was obtained as a yellow, highly viscous oil (12.8 g, 46.9 mmol, 77% yield), which became solid after drying for several hours under high vacuum.

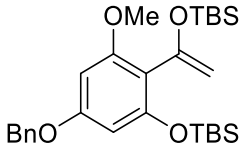
$\mathbf{R}_f$ = 0.54 (petroleum ether/EtOAc 2:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.43 – 7.33 (m, 5H, 5x Ar*H*) 6.14 (d, $\mathcal{J}$ = 2.2 Hz, 1H, Ar*H*), 6.01 (d, $\mathcal{J}$ = 2.2 Hz, 1H, Ar*H*), 5.07 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 203.3 (q, *C*=O), 167.7 (q, Ar*C*), 165.3 (q, Ar*C*), 163.0 (q, Ar*C*), 136.0 (q, Ar*C*), 128.8 (t, 2x Ar*C*), 128.5 (t, Ar*C*H), 127.8 (t, 2x Ar*C*), 106.3 (q, Ar*C*), 94.5 (t, Ar*C*H), 91.4 (t, Ar*C*H), 70.4 (s, *C*H_2), 55.7 (p, O*C*H_3), 33.1 (p, *C*H_3).

The analytical data are consistent with those reported in the literature.[66]

((1-(4-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-6-methoxyphenyl)vinyl)oxy) (*tert*-butyl)dimethylsilane (E3)

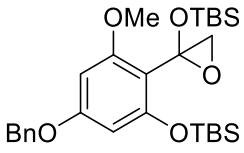


E3
$C_{28}H_{44}O_4Si_2$
MW: 500.83

A solution of 4-benzyloxy-2-hydroxy-6-methoxyacetophenone (**101**) (16.9 g, 62.0 mmol, 1.00 eq.) in CH_2Cl_2 (125 mL) was cooled to 0 °C, treated with triethylamine (21.6 mL, 155 mmol, 2.50 eq.) and TBSOTf (32.8 mL, 143 mmol, 2.30 eq.) and stirred at 0 °C for 2.5 h. The reaction was terminated by the addition $NaHCO_3$ solution (aq., sat.) and was allowed to warm to rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yielding two-phasic mixture of the product and triethylammonium triflate was diluted with Et_2O and NH_4Cl solution (aq., sat.) and the phases were separated. The aqueous phase was extracted with Et_2O (100 mL, 3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Product **E3** was obtained as a salmon-colored solid (31.8 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.76 (petroleum ether/EtOAc 5:1).

((2-(4-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-6-methoxyphenyl)oxiran-2-yl)oxy)(*tert*-butyl)dimethylsilane (E4)

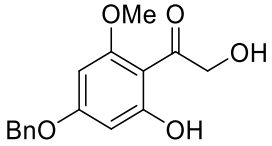


E4
$C_{28}H_{44}O_5Si_2$
MW: 516.83

TBS enol ether **E3** (31.8 g, 62.0 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (60.0 mL) and added to a suspension of *m*CPBA (77 wt%, 21.4 g, 86.8 mmol, 1.40 eq.) and $NaHCO_3$ (11.2 g, 133 mmol, 2.15 eq.) in CH_2Cl_2 (240 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred for 2 h. Then, the reaction mixture was diluted with CH_2Cl_2 (300 mL), washed with $NaHCO_3$ (aq., sat.) and H_2O, dried over $MgSO_4$ and filtered. After concentration under reduced pressure, product **E4** was obtained as a brown viscous oil (32.1 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.53 (petroleum ether/EtOAc 5:1).

1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)-2-hydroxyethan-1-one (106)



106

$C_{16}H_{16}O_5$

MW: 288.30

A solution of crude epoxide **E4** (32.1 g, 62.0 mmol, 1.00 eq.) in THF (320 mL) and H_2O (32.0 mL) was treated with *p*TsOH·H_2O (1.18 g, 6.20 mmol, 10 mol%). The orange reaction mixture was heated under refluxing conditions for 6 h. The mixture was allowed to cool to rt and partitioned between EtOAc and $NaHCO_3$ solution (aq., sat.). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification by column chromatography (petroleum ether/EtOAc 5:1 → 2:1) the desired product **106** was obtained as a pale-brown solid (10.9 g, 37.8 mmol) in 61% yield over three steps.

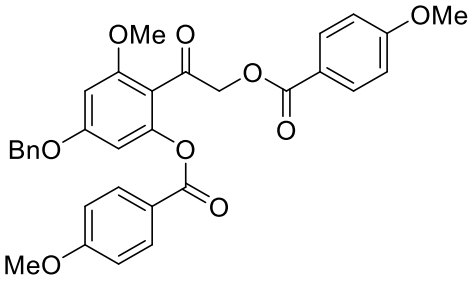
$\mathbf{R}_f$ = 0.21 (petroleum ether/EtOAc 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.21 (s, 1H, O*H*), 7.43 – 7.34 (m, 5H, 5x Ar*H*), 6.19 (d, J = 2.3 Hz, 1H, Ar*H*), 6.02 (d, J = 2.3 Hz, 1H, Ar*H*), 5.08 (s, 2H, CH_2), 4.72 (s, 2H, CH_2OH), 3.86 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 202.1 (q, *C*=O), 167.4 (q, Ar*C*), 166.3 (q, Ar*C*), 163.3 (q, Ar*C*), 135.7 (q, Ar*C*), 128.9 (t, 2x Ar*C*), 128.6 (t, Ar*C*H), 127.8 (t, Ar*C*H), 103.6 (q, Ar*C*), 94.8 (t, Ar*C*H), 91.7 (t, Ar*C*H), 70.6 (s, *C*H_2), 68.8 (s, *C*H_2OH), 55.9 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[66]

2-(4-(Benzyloxy)-2-methoxy-6-((4-methoxybenzoyl)oxy)phenyl)-2-oxoethyl 4-methoxybenzoate (107)



107

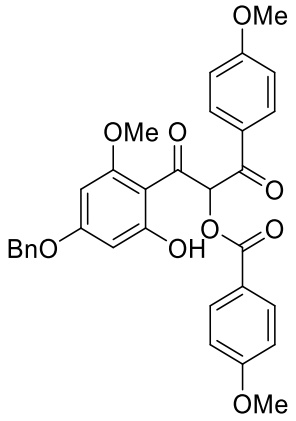
$C_{32}H_{28}O_9$

MW: 556.57

A solution of the α-hydroxy ketone **106** (4.27 g, 14.8 mmol, 1.00 eq.) in CH_2Cl_2 (40.0 mL) was treated with 4-DMAP (90.4 mg, 740 µmol, 5 mol%) and triethylamine (6.19 mL, 44.4 mmol, 3.00 eq.). The mixture was cooled to 0 °C and 4-methoxybenzoyl chloride (4.01 mL, 29.6 mmol, 2.00 eq.) was added and stirred at rt for 3 h. The solution was terminated by the addition of HCl (1.00 M in H_2O.) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired bisbenzoate **107** was obtained as a yellow foam (8.24 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.28 (petroleum ether/EtOAc 2:1).

1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1,3-dioxopropan-2-yl 4-methoxybenzoate (108)

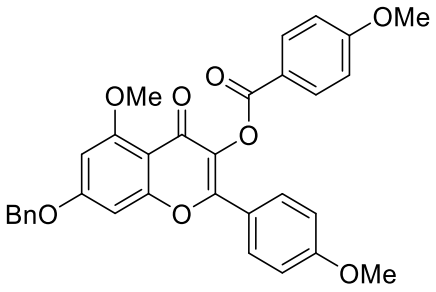


108
$C_{32}H_{28}O_9$
MW: 556.57

A solution of crude bisbenzoate **107** (8.24 g, 14.8 mmol, 1.00 eq.) in THF (80.0 mL) was cooled to –20 °C and treated with LiHMDS (1.00 M in THF, 44.4 mL, 44.4 mmol, 3.00 eq.). The mixture was stirred at –20 °C for 1 h. Then, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.) and warmed to rt. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired phenol **108** was obtained as a yellow foam (8.24 g) and used directly for the next step.

$\mathbf{R}_f$ = 0.30 (petroleum ether/EtOAc 2:1).

7-(Benzyloxy)-5-methoxy-2-(4-methoxyphenyl)-4-oxo-4*H*-chromen-3-yl 4-methoxybenzoate (109)



109
$C_{32}H_{26}O_8$
MW: 538.55

A suspension of crude phenol **108** (8.24 g, 14.8 mmol, 1.00 eq.) in AcOH (170 mL) was treated with H_2SO_4 (96 wt%, 4.11 mL, 74.0 mmol, 5.00 eq.) and stirred at rt for 15 h. The reaction mixture was poured into ice-cold H_2O and stirred for 15 min. Thereby, a pale-pink precipitate was formed. The mixture was filtered on a BÜCHNER funnel and the precipitate was washed with H_2O. The wet solid was suspended in a minimal amount of ethanol and heated to reflux for 1 h. The mixture was allowed to cool to rt, filtered on a BÜCHNER funnel and washed with a small amount of cold ethanol. The solid

was dried under reduced pressure to constant weight to give the desired 3-benzyloxyflavonate **109** as colorless solid (5.85 g, 10.9 mmol) in 73% yield over three steps.

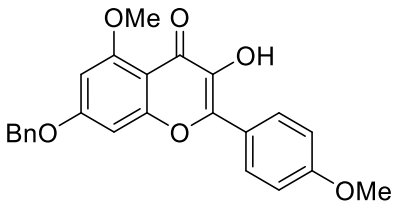
$\mathbf{R}_f$ = 0.28 (petroleum ether/EtOAc 1:2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.16 (d, J = 8.8 Hz, 2H, 2x Ar*H*), 7.87 (d, J = 9.0 Hz, 2H, 2x Ar*H*), 7.48 – 7.38 (m, 5H, 5x Ar*H*), 6.97 – 6.93 (m, 4H, 4x Ar*H*), 6.63 (d, J = 2.2 Hz, 1H, Ar*H*), 6.44 (d, J = 2.2 Hz, 1H, Ar*H*), 5.16 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.9 (q, *C*=O), 164.0 (q, Ar*C*), 163.9 (q, Ar*C*), 163.4 (q, O*C*=O), 161.7 (q, Ar*C*), 161.5 (q, Ar*C*), 159.3 (q, Ar*C*), 153.5 (q, *C*=C-C=O), 135.8 (q, Ar*C*), 134.1 (q, O=C-*C*=C), 132.9 (t, 2x Ar*C*), 129.8 (t, 2x Ar*C*), 129.0 (t, 2x Ar*C*), 128.6 (t, Ar*C*H), 127.8 (t, 2x Ar*C*), 122.5 (q, Ar*C*), 121.6 (q, Ar*C*), 114.2 (t, 2x Ar*C*), 113.9 (t, 2x Ar*C*H), 109.2 (q, Ar*C*), 96.7 (t, Ar*C*H), 93.6 (t, Ar*C*H), 70.7 (s, *C*H_2), 56.4 (p, O*C*H_3), 55.6 (p, O*C*H_3), 55.5 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[66]

7-(Benzyloxy)-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (102)



102
$C_{24}H_{20}O_6$
MW: 404.42

A suspension of the benzoate **109** (5.85 g, 10.9 mmol, 1.00 eq.) in EtOH (135 mL) was treated with NaOH solution (5 wt% in H_2O, 15.5 mL, 20.4 mmol, 1.88 eq.). The yellowish suspension was stirred at 80 °C for 1 h. The reaction mixture was allowed to cool to rt and was neutralized with HCl (1.00 M in H_2O, 20.4 mL, 20.4 mmol, 1.88 eq.). The resulting suspension was filtered on a BÜCHNER funnel and the precipitate was washed with a small amount of cold ethanol. The solid was dried under reduced pressure to constant weight to give the desired 3-hydroxyflavone **102** as a yellowish solid (4.05 g, 10.0 mmol) in 92% yield.

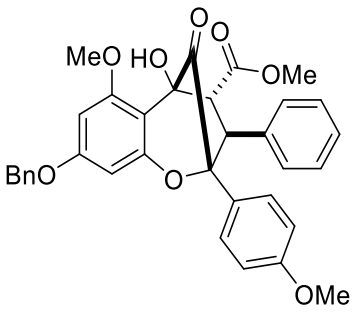
$\mathbf{R}_f$ = 0.35 (petroleum ether/EtOAc 1:2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.17 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 7.48 – 7.38 (m, 5H, 5x Ar*H*), 7.36 (bs, 1H, O*H*), 7.03 (d, J = 9.0 Hz, 2H, 2x Ar*H*), 6.63 (d, J = 1.9 Hz, 1H, Ar*H*), 6.43 (d, J = 1.8 Hz, 1H, Ar*H*), 5.15 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.0 (q, *C*=O), 163.5 (q, Ar*C*), 160.8 (q, Ar*C*), 160.7 (q, Ar*C*), 158.9 (q, Ar*C*), 142.4 (q, *C*=COH), 137.6 (q, *C*OH), 135.7 (q, Ar*C*), 129.0 (t, 2x Ar*C*), 128.9 (t, 2x Ar*C*), 128.6 (t, Ar*C*H), 127.8 (t, 2x Ar*C*), 123.7 (q. Ar*C*), 114.1 (t, 2x Ar*C*), 106.5 (q, Ar*C*), 96.3 (t, Ar*C*H), 93.5 (t, Ar*C*H), 70.7 (s. *C*H_2), 56.6 (p, O*C*H_3), 55.5 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[66]

(±)-Methyl (3*S*,4*S*,5*R*)-8-(benzyloxy)-5-hydroxy-6-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E5)

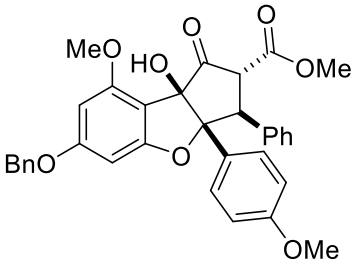


E5
$C_{34}H_{30}O_8$
MW: 566.61

Methyl cinnamate (6.14 g, 37.9 mmol, 14.2 eq.) was added to a solution of flavonol **102** (1.01 g, 2.67 mmol, 1.00 eq.) in dry chloroform (51.2 mL) and freshly distilled 2,2,2-trifluoroethanol (22.0 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure and the remaining amount of methyl cinnamate was removed by column chromatography (petroleum ether/EtOAc 4:1 ⟶ 1:1). Product **E5** was obtained as a mixture of isomers as a yellowish foam (1.37 g) and used directly for the next step.

$\mathbf{R}_f$ = 0.20 − 0.40 (petroleum ether/EtOAc 1:2).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)- 6-(benzyloxy)-8b-hydroxy-8-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E6)

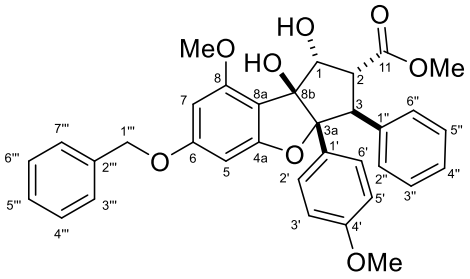


E6
$C_{34}H_{30}O_8$
MW: 566.61

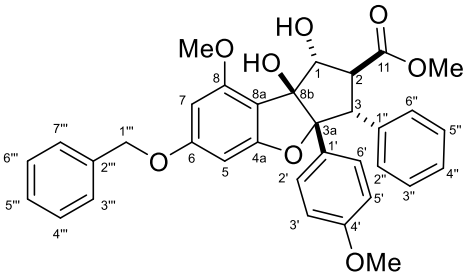
Cycloadduct **E5** (1.37 g, 2.41 mmol, 1.00 eq.) was dissolved in MeOH (80.0 mL). Then NaOMe solution (25 wt% in MeOH, 1.10 mL, 6.85 mmol, 2.84 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Product **E6** was obtained as a mixture of isomers as a yellow, glassy foam (1.33 g) and used directly for the next step.

$\mathbf{R}_f$ = 0.49 (petroleum ether/EtOAc 1:2).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-*endo*-103)



(±)-*endo*-103



(±)-*exo*-103

$C_{34}H_{32}O_8$
MW: 568.62

A mixture of $(CH_3)_4N(OAc)_3BH$ (2.08 g, 7.90 mmol, 6.42 eq.) and freshly distilled AcOH (732 µL, 12.8 mmol, 10.4 eq.) in MeCN (32.0 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E6** (697 mg, 1.23 mmol, 1.00 eq.) in MeCN (21.3 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (petroleum ether/EtOAc 3:2) was then performed to obtain the racemic *endo*-product **(±)-*endo*-103** as a pale-yellow solid (423 mg, 744 µmol) in 56% yield over 3 steps. In addition, the racemic *exo*-product **(±)-*exo*-103** was obtained as a pale-yellow solid (202 mg, 355 µmol) in 27% yield over 3 steps.

(±)-*endo*-103:

R$_f$ = 0.63 (petroleum ether/EtOAc 1:2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.47 – 7.35 (m, 5H, *H*-3’’’, *H*-4’’’, *H*-5’’’, *H*-6’’’, *H*-7’’’), 7.11 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-2’, *H*-6’), 7.08 – 7.05 (m, 3H, *H*-3’’, *H*-4’’, *H*-5’’), 6.88 – 6.86 (m, 2H, *H*-2’’, *H*-6’’), 6.68 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-3’, *H*-5’), 6.36 (d, $\mathcal{J}$ = 1.9 Hz, 1H, *H*-5), 6.22 (d, $\mathcal{J}$ = 1.9 Hz, 1H, *H*-7), 5.09 (s, 2H, *H*-1’’’), 5.03 (dd, $\mathcal{J}$ = 6.7, 1.6 Hz, 1H, *H*-1), 4.31 (d, $\mathcal{J}$ = 14.2 Hz, 1H, *H*-3), 3.90 (dd, $\mathcal{J}$ = 14.4, 6.5 Hz, 1H, *H*-2), 3.86 (s, 3H, C*H*$_3$O-8), 3.71 (s, 3H, C*H*$_3$O-4’), 3.67 (br, 1H, O*H*-8b), 3.65 (s, 3H, C*H*$_3$O-11), 1.77 (s, 1H, O*H*-1).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.7 (q, *C*-11), 163.4 (q, *C*-6), 161.0 (q, *C*-4a), 158.9 (q, *C*-4’), 157.1 (q, *C*-8), 137.0 (q, *C*-1’’), 136.6 (q, *C*-2’’’), 129.1 (t, *C*-3’, *C*-5’), 128.8 (t, *C*-4’’’, *C*-6’’’), 128.3 (t, *C*-5’’’), 128.0 (t, *C*-3’’, *C*-5’’), 127.9 (t, *C*-2’’, *C*-6’’), 127.7 (t, *C*-3’’’, *C*-7’’’), 126.7 (t, *C*-4’’), 126.5 (q. *C*-1’), 112.9 (t, *C*-3’, *C*-5’), 108.1 (q, *C*-8a), 102.0 (q, *C*-3a), 93.8 (q, *C*-8b), 93.5 (t, *C*-7), 90.6 (t, *C*-5), 79.7 (t, *C*-1), 70.6 (s, *C*-1’’’), 55.9 (p, H$_3$*C*O-8), 55.3 (p, H$_3$*C*O-4’), 55.1 (t, *C*-3), 52.1 (p, H$_3$*C*O-11), 50.6 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{34}H_{32}O_8Na$ $[M+Na]^+$ 591.1995, found 591.1987.

The analytical data are consistent with those reported in the literature.[66]

(±)-*exo*-103:

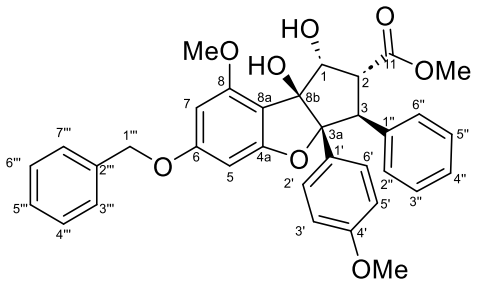
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.48 – 7.33 (m, 5H, *H*-3''', *H*-4''', *H*-5''', *H*-6''', *H*-7''', *H*-8'''), 7.23 (dt, $\mathcal{J}$ = 9.9, 2.5 Hz, 2H, *H*-2', *H*-6'), 7.18 – 7.13 (m, 3H, *H*-3'', *H*-4'', *H*-5''), 6.93 – 6.90 (m, 2H, *H*-2'', *H*-6''), 6.87 (dt, $\mathcal{J}$ = 9.6, 2.6 Hz, 2H, *H*-3', *H*-5'), 6.26 (d, $\mathcal{J}$ = 2.0 Hz, 1H, *H*-5), 6.21 (d, $\mathcal{J}$ = 2.0 Hz, 1H, *H*-7), 5.20 (s, 1H, O*H*-8b), 5.09 (s, 2H, *H*-1'''), 5.07 (d, $\mathcal{J}$ = 4.9 Hz, 1H, O*H*-1), 4.51 (dd, $\mathcal{J}$ = 10.4, 5.0 Hz, 1H, *H*-1), 3.81 (d, $\mathcal{J}$ = 12.8 Hz, 1H, *H*-3), 3.72 (s, 3H, C*H*$_3$O-4'), 3.68 (s, 3H, C*H*$_3$O-8), 3.47 (s, 3H, C*H*$_3$O-11), 2.98 (dd, $\mathcal{J}$ = 12.8, 10.4 Hz, 1H, *H*-2).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 173.1 (q, *C*-11), 161.6 (q, *C*-6), 161.0 (q, *C*-4a), 159.0 (q, *C*-8), 158.2 (q, *C*-4'), 137.0 (q, *C*-1''), 135.6 (q, *C*-2'''), 130.1 (t, *C*-4''), 128.8 (t, *C*-2', *C*-6'), 128.4 (t, *C*-4''', *C*-6'''), 128.3 (t, *C*-2'', *C*-6''), 127.88 (t, *C*-5'''), 127.86 (t, C-3''', C-7'''), 127.76 (t, C-3'', C-5''), 126.9 (q, *C*-1'), 112.7 (t, *C*-3', *C*-5'), 106.4 (q, *C*-8a), 99.0 (q, *C*-3a), 93.0 (t, *C*-5), 90.5 (q, *C*-8b), 88.6 (t, *C*-7), 83.5 (t, *C*-1), 69.6 (t, *C*-1'''), 55.4 (p, H$_3$*C*O-8), 55.0 (p, H$_3$*C*O-4'), 53.7 (t, *C*-3), 51.6 (p, H$_3$*C*O-11), 50.8 (t, *C*-2).

R$_f$ = 0.50 (petroleum ether/EtOAc 1:2).

The analytical data are consistent with those reported in the literature.[66]

Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((–)-*endo*-103)

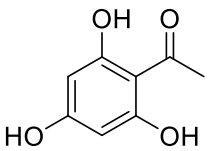


(–)-*endo*-103
$C_{34}H_{32}O_8$
MW: 568.62

Racemic **(±)-*endo*-106** (30.0 mg, 52.8 µmol) was subjected to chiral HPLC separation (5 µm PHENOMENEX Lux Cellulose-1 preparative column: 250 x 21.2 mm, MeCN/H_2O 30% ⟶ 70%, flow rate: 20.0 mL/min) to provide the active enantiomer **(–)-*endo*-103** (13.1 mg, 23.0 µmol, 44%) (t_R = 49.69 min) as a colorless solid.

[α]$_D^{27}$ = –50.8° (*c* 0.26, CH_2Cl_2) (lit.[90] [α]$_D^{23}$ = –51.2° (*c* 0.48, CH_2Cl_2)).

1-(2,4,6-Trihydroxyphenyl)ethan-1-one (112)



112
$C_8H_8O_4$
MW: 168.15

To a solution of phloroglucinol (**111**) (10.0 g, 79.3 mmol, 1.00 eq.) and acetic anhydride (10.0 mL, 106 mmol, 1.34 eq.) in EtOAc (40.0 mL), $BF_3{\cdot}Et_2O$ (8.03 mL, 65.0 mmol, 0.83 eq.) was added dropwise.

The reaction mixture was stirred at 40 °C for 16 h. Then, the reaction mixture was diluted with H_2O (100 mL) and the layers were separated. The aqueous layers were extracted with EtOAc (3x). The combined organic layers were washed with $NaHCO_3$ solution (aq., sat.), dried over $MgSO_4$ and filtered. After evaporation of the solvent, H_2O (400 mL) was added to the yellowish solid. The suspension was heated under refluxing conditions for 5 min and cooled down to rt. After filtration and drying, the desired product **112** was collected as a pale-orange solid (10.9 g, 65.1 mmol) in 82% yield.

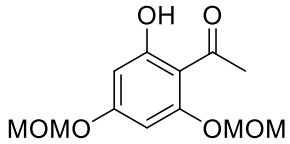
$\mathbf{R}_f$ = 0.29 (petroleum ether/EtOAc 2:3).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 12.22 (s, 2H, 2x O*H*), 10.36 (s, 1H, O*H*), 5.79 (s, 2H, 2x Ar*H*), 2.54 (s, 3H, CH_3).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 202.5 (q, *C*=O), 164.8 (q, Ar*C*), 164.3 (q, 2x Ar*C*), 104.9 (q, Ar*C*), 94.5 (t, 2x Ar*C*), 32.4 (p, *C*H_3).

The analytical data are consistent with those reported in the literature.[227]

1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)ethan-1-one (113)



113

$C_{12}H_{16}O_6$

MW: 256.25

To the solution of acetophenone **112** (10.0 g, 59.5 mmol, 1.00 eq.) in CH_2Cl_2 (216 mL) were added *i*Pr$_2$NEt (46.0 mL, 271 mmol, 4.55 eq.) and MOMCl (16.7 mL, 220 mmol, 3.70 eq.) at 0 °C. Then, the resulting mixture was allowed to warm to rt and was stirred for 30 min. Subsequently, the reaction mixture was terminated by the addition of $NaHCO_3$ solution (aq., sat.) and extracted with EtOAc. The organic layer was washed with NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (petroleum ether/EtOAc 5:1) to afford the desired product **113** as a yellowish oil (10.8 g, 42.3 mmol) in 71% yield.

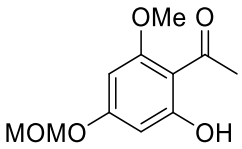
$\mathbf{R}_f$ = 0.41 (petroleum ether/EtOAc 2:3).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.23 (dd, J = 7.0, 2.3 Hz, 2H, 2x Ar*H*), 5.25 (s, 2H, OCH_2O), 5.15 (s, 2H, OCH_2O), 3.50 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 2.64 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 203.3 (q, *C*=O), 166.9 (q, Ar*C*), 163.5 (q, Ar*C*), 160.5 (q, Ar*C*), 107.0 (q, Ar*C*), 97.2 (t, Ar*C*H), 94.6 (t, Ar*C*H), 94.1 (s, 2x O*C*H$_2$O), 56.8 (p, O*C*H$_3$), 56.5 (p, O*C*H$_3$), 33.1 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[228]

1-(2-Hydroxy-6-methoxy-4-(methoxymethoxy)phenyl)ethan-1-one (114)



114
$C_{11}H_{14}O_5$
MW: 226.23

To a solution of the MOM-protected acetophenone **113** (10.7 g, 41.6 mmol, 1.00 eq.) in anhydrous acetone (75.7 mL) were added K_2CO_3 (17.3 g, 125 mmol, 3.00 eq.) and Me_2SO_4 (4.23 ml, 44.7 mmol, 1.08 eq.). The suspension was heated under refluxing conditions for 2 h, then terminated by addition of H_2O (100 mL) and extracted with Et_2O (3x 150 mL). The combined organic layers were washed with NaCl solution (aq., sat.), dried over $MgSO_4$ and filtered. The filtrate was concentrated to furnish a yellow residue that was dissolved in a mixture of MeOH (83.2 mL) and HCl (1.00 M in H_2O, 25.0 mL, 4.16 mmol, 10 mol%) at rt. After stirring at 30 °C for 12 h, the resulting mixture was allowed to cool to rt, filtered and washed with ice-cold MeOH (83.2 mL). The mother liquor was concentrated until the formation of a precipitation was visible, cooled to 0 °C and filtered a second time. The combined residues were dried under reduced pressure to afford the desired product **114** as a colorless solid (5.37 g, 23.7 mmol) in 57% yield.

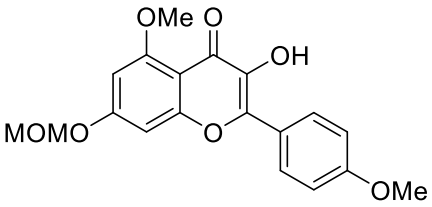
$\mathbf{R}_f$ = 0.48 (petroleum ether/EtOAc 2:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.21 (d, J = 2.2 Hz, 1H, Ar*H*), 6.03 (d, J = 2.2 Hz, 1H, Ar*H*), 5.18 (s, 2H, OC*H*$_2$O), 3.86 (s, 3H, OCH$_2$OC*H*$_3$), 3.47 (s, 3H, OC*H*$_3$), 2.61 (s, 3H, C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 203.5 (q, *C*=O), 167.2 (q, Ar*C*), 163.7 (q, Ar*C*), 163.2 (q, Ar*C*), 106.7 (q, Ar*C*), 96.4 (t, Ar*C*H), 94.1 (s, O*C*H$_2$O), 91.4 (t, Ar*C*H), 56.6 (p, O*C*H$_3$), 55.7 (p, OCH$_2$O*C*H$_3$), 33.2 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[228]

3-Hydroxy-5-methoxy-7-(methoxymethoxy)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (115)



115
$C_{19}H_{18}O_7$
MW: 358.35

An Erlenmeyer flask was charged with a relatively large stirring bar, H_2O (83.4 mL) and pyrrolidine (4.11 mL, 50.0 mmol, 10.0 eq.). At maximum stirring speed, 4-methoxybenzaldehyde (639 µL, 5.25 mmol, 1.05 eq.) was added. After stirring for 5 min at rt, the finely grounded acetophenone **114** (1.13 g, 5.00 mmol, 1.00 eq.) was added in portions. The resulting mixture was stirred at 50 °C for 24 h and then cooled to rt, subsequently poured into ice-cold H_2O and acidified to pH = 4 with HCl (37 wt%,

aq.). The resulting precipitate was filtered and washed with H_2O. The crude product was recrystallized from aqueous ethanol (*v/v* 80%) to afford the desired flavonol **115** as a yellowish solid (850 mg, 2.37 mmol) in 47% yield.

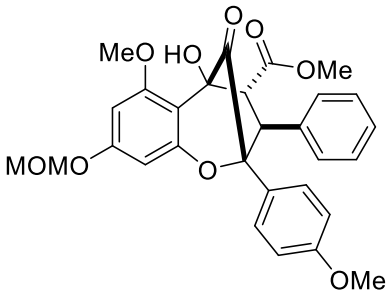
$\mathbf{R}_f$ = 0.31 (petroleum ether/EtOAc 1:2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.18 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 7.03 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 6.78 (d, J = 1.9 Hz, 1H, Ar*H*), 6.44 (d, J = 1.8 Hz, 1H, Ar*H*), 5.28 (s, 2H, OCH_2O), 3.99 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_2OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.1 (q, *C*=O), 161.9 (q, Ar*C*), 160.8 (q, Ar*C*), 160.7 (q, Ar*C*), 158.7 (q, Ar*C*), 142.6 (q, *C*=COH), 137.6 (q, *C*OH), 129.1 (t, 2x Ar*C*), 123.7 (q. Ar*C*), 114.1 (t, 2x Ar*C*), 106.9 (q, Ar*C*), 96.5 (t, Ar*C*H), 95.4 (t, Ar*C*H), 94.5 (s, O*C*H_2O), 56.7 (p, OCH_2OCH_3), 56.6 (p, O*C*H_3), 55.5 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[62]

(±)-Methyl (3*S*,4*S*,5*R*)-8-(methoxymethoxy)-5-hydroxy-6-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E7)

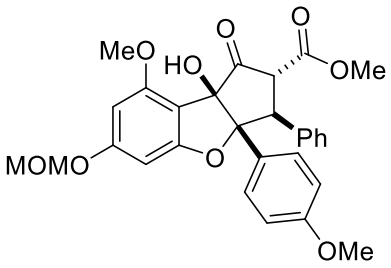


E7
$C_{29}H_{28}O_9$
MW: 520.53

Methyl cinnamate (2.88 g, 17.8 mmol, 14.2 eq.) was added to a solution of flavonol **115** (448 mg, 1.25 mmol, 1.00 eq.) in dry chloroform (24.5 mL) and freshly distilled 2,2,2-trifluoroethanol (10.4 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (48 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 4:1 ⟶ 1:1). Product **E7** was obtained as a mixture of isomers as a yellowish foam (461 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.43 − 0.61 (petroleum ether/EtOAc 1:2).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)- 8b-hydroxy-8-methoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E8)

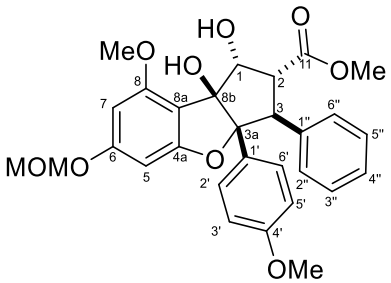


E8
$C_{29}H_{28}O_9$
MW: 520.53

Cycloadduct **E7** (461 mg, 886 µmol, 1.00 eq.) was dissolved in MeOH (32.8 mL). Then NaOMe solution (478 µL, 25 wt% in MeOH, 2.88 mmol, 2.84 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Product **E8** was obtained as a mixture of isomers as a yellow, glassy foam (461 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.38 (petroleum ether/EtOAc 1:2).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-116)



(±)-116
$C_{29}H_{30}O_9$
MW: 522.55

A mixture of $(CH_3)_4N(OAc)_3BH$ (1.50 g, 5.69 mmol, 6.42 eq.) and freshly distilled AcOH (527 µL, 9.22 mmol, 10.4 eq.) in MeCN (23.0 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E8** (461 mg, 886 µmol, 1.00 eq.) in MeCN (15.3 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (petroleum ether/EtOAc 4:1 ⟶ 1:1) was then performed to obtain the racemic *endo*-product **(±)-116** as a pale-yellow foam (220 mg, 421 µmol) in a yield of 34% over 3 steps.

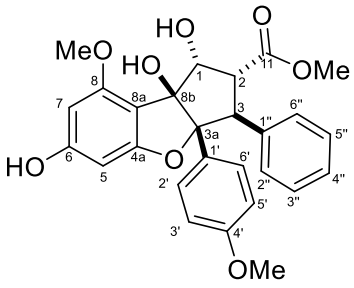
$\mathbf{R}_f$ = 0.42 (petroleum ether/EtOAc 1:2).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.11 (dt, J = 9.9, 2.5 Hz, 2H, *H*-2', *H*-6'), 7.07 – 7.04 (m, 3H, *C*-2'', *C*-4'', *C*-6''), 6.88 – 6.86 (m, 2H, *C*-3'', *C*-5''), 6.67 (dt, J = 10.0, 2.5 Hz, 2H, *C*-3', *C*-5'), 6.46 (d, J = 1.8 Hz, 1H, *H*-5), 6.24 (d, J = 1.9 Hz, 1H, *H*-7), 5.19 (d, J = 0.8 Hz, 2H, O*C*H_2O-6), 5.04 (d, J = 6.7 Hz, 1H, *H*-1), 4.30 (d, J = 14.2 Hz, 1H, *H*-3), 3.90 (dd, J = 14.0, 6.6 Hz, 1H, *H*-2), 3.88 (s, 3H, *H*$_3$CO-8), 3.71 (s, 3H, C*H*$_3$O-4'), 3.69 (bs, 1H, *H*O-8b), 3.65 (s, 3H, *H*$_3$CO-11), 3.51 (s, 3H, *H*$_3$COCH_2O-6), 1.81 (bs, 1H, *H*O-1).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 170.7 (q, *C*-11), 161.7 (q, *C*-6), 160.8 (q, *C*-4a), 158.9 (q, *C*-4'), 157.1 (q, *C*-8), 137.0 (q, *C*-1''), 129.1 (t, *C*-2', *C*-6'), 128.0 (t, *C*-3'', *C*-5''), 127.9 (t, *C*-2'', *C*-6''), 126.7 (t, *C*-4''), 126.5 (q, *C*-1'), 112.9 (t, *C*-3', *C*-5'), 109.0 (q, *C*-8a), 102.0 (q, *C*-3a), 94.7 (s, O*C*H_2O-6), 94.0 (t, *C*-7), 93.8 (q, *C*-8b), 92.7 (t, *C*-5), 79.8 (t, *C*-1), 56.3 (p, H$_3$*C*OCH_2O-6), 56.0 (p, H$_3$*C*O-8), 55.3 (p, H$_3$*C*O-4'), 55.1 (t, *C*-3), 52.1 (p, H$_3$*C*O-11), 50.6 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[62]

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,6,8b-trihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-110)



(±)-110
$C_{27}H_{26}O_8$
MW: 478.50

Method A from 6-Bn-protected *endo*-methyl rocaglate ((±)-*endo*-103)

Palladium on carbon (10 wt%, 58.8 mg, 55.2 µmol, 10 mol%) was added to a solution of benzyl ether **(±)-*endo*-103** (314 mg, 552 µmol, 1.00 eq.) in dry THF (5.52 mL) under an argon atmosphere. The atmosphere was replaced by hydrogen and an additional balloon of hydrogen was placed on the flask. The reaction mixture was stirred for 200 min at rt and then filtered over Celite®. The filtrate was concentrated to dryness and gave the desired phenol **(±)-110** as a colorless foam (255 mg, 533 µmol) in 97% yield.

Method B from 6-MOM-protected *endo*-methyl rocaglate ((±)-116)

To a solution of methoxymethyl ether **(±)-116** (66.0 mg, 126 µmol, 1.00 eq.) in CH_2Cl_2 (2.81 mL) at −78 °C was added dropwise a solution of trimethylsilyl bromide (2.00 M in CH_2Cl_2, 316 µL, 632 µmol, 5.00 eq.) in two aliquots over 2 h. The reaction mixture was then allowed to warm to −50 °C and stirred for additional 6 h, then terminated by the addition of H_2O (10.0 mL) and extracted with CH_2Cl_2 (2x 10.0 mL). The combined organic extracts were washed with NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification by column chromatography (petroleum ether/EtOAc 3:1 ⟶ 1:1) to afford the desired phenol **(±)-110** as a colorless foam (36.3 mg, 75.9 µmol) in 60% yield.

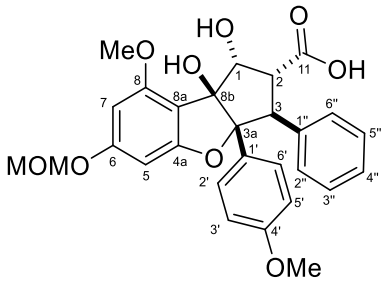
$\mathbf{R}_f$ = 0.16 (petroleum ether/EtOAc 1:1).

^{1}H-NMR (acetone-d_6, 400 MHz): δ [ppm] 8.61 (s, 1H, O*H*-6), 7.12 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-2', *H*-6'), 7.06 – 6.92 (m, 3H, *H*-3'', *H*-4'', *H*-5''), 6.92-6.90 (m, 2H, *H*-2'', *H*-6''), 6.63 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 6.16 (d, $\mathcal{J}$ = 1.9 Hz, 1H, *H*-5), 6.11 (d, $\mathcal{J}$ = 1.8 Hz, 1H, *H*-7), 4.93 (dd, $\mathcal{J}$ = 6.4, 2.8 Hz, 1H, *H*-1), 4.28 (d, $\mathcal{J}$ = 14.1 Hz, 1H, *H*-3), 3.97 (s, 1H, O*H*-8b), 3.94 (ddd, $\mathcal{J}$ = 14.1, 6.6, 0.8 Hz, 1H, *H*-2), 3.83 (s, 3H, CH_3O-4'), 3.66 (s, 3H, CH_3O-8), 3.56 (s, 3H, CH_3O-11).

^{13}C-NMR (acetone-d_6, 100 MHz): δ [ppm] 170.8 (q, *C*-11), 162.1 (q, *C*-6), 161.8 (q, *C*-4a), 159.3 (q, *C*-4'), 158.7 (q, *C*-8), 139.2 (q, *C*-1''), 130.0 (t, C-2', C-6'), 128.9 (q, *C*-1'), 128.8 (t, *C*-3'', *C*-5''), 128.2 (t, *C*-2'', *C*-6''), 126.8 (t, *C*-4''), 112.8 (t, *C*-3', *C*-5'), 108.4 (q, *C*-8a), 102.6 (q, *C*-3a), 94.5 (q, *C*-8b), 93.2 (t, *C*-7), 91.9 (t, *C*-5), 80.8 (t, *C*-1), 55.9 (p, H$_3$*C*O-8), 55.7 (t, *C*-3), 55.2 (p, H$_3$*C*O-4'), 52.6 (p, H$_3$*C*O-11), 51.2 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[229]

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (E9)



E9

$C_{28}H_{28}O_9$

MW: 508.52

A solution of methyl ester **(±)-116** (207 mg, 396 µmol, 1.00 eq.) and lithium hydroxide (2.00 M in H_2O, 1.01 mL, 2.02 mmol, 5.10 eq.) in MeOH (6.19 mL) was heated at 50 °C for 5 h. The solution was allowed to cool to rt, acidified with HCl (1.00 M in H_2O) to pH 1-2 and diluted with CH_2Cl_2 (25.0 mL) and H_2O (25.0 mL). The organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2x 25.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the rocagloic acid **E9** as a yellowish solid (200 mg, 393 µmol) in 99% yield.

$\mathbf{R}_f$ = 0.24 (EtOAc).

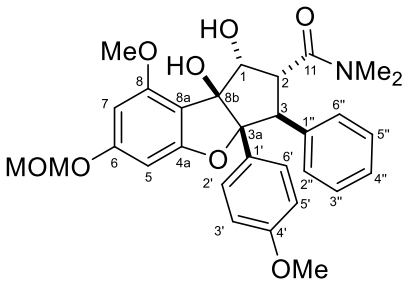
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.09 – 7.04 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.86 – 6.85 (m, 2H, *H*-2'', *H*-6''), 6.66 (d, $\mathcal{J}$ = 8.8 Hz, 2H, *H*-3', *H*-5'), 6.44 (d, $\mathcal{J}$ = 1.6 Hz, 1H, *H*-5), 6.22 (d, $\mathcal{J}$ = 1.6 Hz, 1H, *H*-7), 5.17 (d, $\mathcal{J}$ = 0.8 Hz, 2H, OCH_2O-6), 5.04 (d, $\mathcal{J}$ = 6.6 Hz, 1H, *H*-1), 4.23 (d, $\mathcal{J}$ = 14.1 Hz, 1H, *H*-3), 3.88 (dd, $\mathcal{J}$ = 14.2, 6.7 Hz, 1H, *H*-2), 3.85 (s, 3H, H_3CO-8), 3.70 (s, 3H, CH_3O-4'), 3.49 (s, 3H, H_3COCH$_2$O-6), 1.84 (bs, 1H, *H*O-1).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 174.2 (q, *C*-11), 161.7 (q, *C*-6), 160.7 (q, *C*-4a), 158.9 (q, *C*-4'), 157.0 (q, *C*-8), 136.6 (q, *C*-1''), 129.1 (t, *C*-2', *C*-6'), 128.0 (t, *C*-3'', *C*-5''), 127.9 (t, *C*-2'', *C*-6''), 126.8 (t, *C*-4''), 126.3 (q, *C*-1'), 112.9 (t, *C*-3', *C*-5'), 108.8 (q, *C*-8a), 101.9 (q, *C*-3a), 94.7 (s, O*C*H$_2$O-6), 94.0 (t, *C*-7), 93.7

(q, *C*-8b), 92.7 (t, *C*-5), 79.5 (t, *C*-1), 56.3 (p, H_3COCH_2O-6), 55.9 (p, H_3CO-8), 55.2 (p, H_3CO-4'), 55.1 (t, *C*-3), 50.2 (t, *C*-2).

HRMS (ESI$^-$) *m/z* calcd. for $C_{28}H_{27}O_9$ $[M-H]^-$ 507.1655, found 507.1670.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-117)



(±)-117
$C_{30}H_{33}NO_8$
MW: 535.59

To a solution of rocagloic acid **E9** (40.0 mg, 78.7 µmol, 1.00 eq.) in CH_2Cl_2 (5.58 mL) EDC·HCl (22.6 mg, 118 µmol, 1.50 eq.), HOBt·H_2O (16.1 mg, 102 µmol, 1.30 eq.), dimethylamine hydrochloride (32.1 mg, 393 µmol, 5.00 eq.) and triethylamine (54.5 µL, 393 µmol, 5.00 eq.) were added. The mixture was then stirred at rt for 12 h. Subsequently, the reaction was terminated by the addition of HCl (1.00 M in H_2O) and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 98:2). The desired rocagloic amide **(±)-117** was obtained as a light-yellow foam (21.9 mg, 40.9 µmol) in 52% yield.

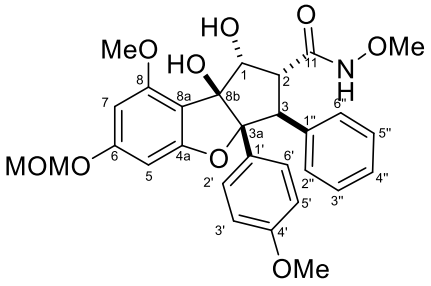
R$_f$ = 0.50 (CH_2Cl_2/MeOH 95:5).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.05 – 6.93 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.82 (d, $\mathcal{J}$ = 7.6 Hz, 2H, *H*-2'', *H*-6''), 6.61 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-3', *H*-5'), 6.37 (d, $\mathcal{J}$ = 1.8 Hz, 1H, *H*-5), 6.24 (d, $\mathcal{J}$ = 1.7 Hz, 1H, *H*-7), 5.22 (s, 2H, OCH_2O-6), 5.08 (s, 1H, O*H*-8b), 4.81 (dd, $\mathcal{J}$ = 6.1, 3.8 Hz, 1H, *H*-1), 4.62 (d, $\mathcal{J}$ = 3.7 Hz, 1H, O*H*-1), 4.22 (d, $\mathcal{J}$ = 13.5 Hz, 1H, *H*-3), 4.02 (dd, $\mathcal{J}$ = 13.4, 6.4 Hz, 1H, *H*-2), 3.80 (p, H_3CO-8), 3.61 (s, 3H, H_3CO-4'), 3.42 (s, 3H, H_3COCH_2O-6), 3.24 (s, 3H, NCH_3), 2.74 (s, 3H, NCH_3).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 168.5 (q, *C*-11), 160.1 (q, *C*-6), 160.0 (q, *C*-4a), 157.7 (q, *C*-8), 157.5 (q, *C*-4'), 139.1 (q, *C*-1''), 128.8 (t, C-2', C-6'), 128.6 (q. *C*-1'), 127.7 (t, *C*-3'', *C*-5''), 127.2 (t, C-2'', C-6''), 125.5 (t, C-4''), 111.9 (t, *C*-3', *C*-5'), 110.0 (q, *C*-8a), 101.2 (q, *C*-3a), 94.0 (t, *C*-7), 93.5 (s, OCH_2O-6 and q, *C*-8b), 91.2 (t, *C*-5), 78.2 (t, *C*-1), 55.7 (p, H_3COCH_2O-6), 55.5 (p, H_3CO-8), 55.3 (t, *C*-3), 54.8 (p, H_3CO-4'), 47.9 (t, *C*-2), 36.4 (p, NCH_3), 35.1(p, NCH_3).

HRMS (ESI$^+$) *m/z* calcd. for $C_{30}H_{33}NO_8Na$ $[M+Na]^+$ 558.2097, found 558.2104.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-*N*,8-dimethoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-118)



(±)-118
$C_{29}H_{31}NO_9$
MW: 537.57

To a solution of rocagloic acid **E9** (40.0 mg, 78.7 µmol, 1.00 eq.) in CH_2Cl_2 (5.58 mL) EDC·HCl (22.6 mg, 118 µmol, 1.50 eq.), HOBt·H_2O (16.1 mg, 102 µmol, 1.30 eq.), methoxylamine hydrochloride (32.8 mg, 393 µmol, 5.00 eq.) and triethylamine (54.5 µL, 393 µmol, 5.00 eq.) were added. The mixture was then stirred at rt for 12 h. Subsequently, the reaction was terminated by the addition of HCl (1.00 M in H_2O), extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 95:5). The desired rocagloic amide **(±)-118** was obtained as a yellowish foam (20.0 mg, 37.2 µmol) in 47% yield.

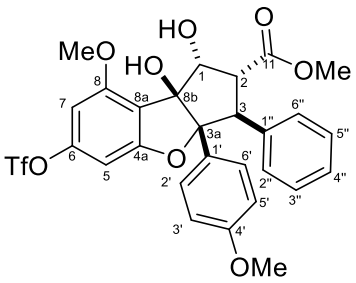
$\mathbf{R}_f$ = 0.33 (CH_2Cl_2/MeOH 95:5).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 11.15 (s, 1H, N*H*OCH$_3$), 7.06 – 6.96 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.89 (d, $\mathcal{J}$ = 7.3 Hz, 2H, *H*-2'', *H*-6''), 6.60 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-3', *H*-5'), 6.34 (d, $\mathcal{J}$ = 1.8 Hz, 1H, *H*-5), 6.21 (d, $\mathcal{J}$ = 1.8 Hz, 1H, *H*-7), 5.21 (s, 2H, OC*H*$_2$O-6), 5.05 (s, 1H, O*H*-8b), 4.70 (d, $\mathcal{J}$ = 4.0 Hz, 1H, O*H*-1), 4.56 (t, $\mathcal{J}$ = 4.8 Hz, 1H, *H*-1), 4.18 (d, $\mathcal{J}$ = 14.1 Hz, 1H, *H*-3), 3.74 (p, *H*$_3$CO-8), 3.60 (s, 3H, *H*$_3$CO-4'), 3.58 (dd, $\mathcal{J}$ = 14.5, 5.6 Hz, 1H, *H*-2), 3.49 (s, 3H, NHOC*H*$_3$), 3.42 (s, 3H, *H*$_3$COCH$_2$O-6).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 166.4 (q, *C*-11), 160.3 (q, *C*-6), 159.9 (q, *C*-4a), 157.8 (q, *C*-8), 157.5 (q, *C*-4'), 138.3 (q, *C*-1''), 128.7 (t, C-2', C-6'), 128.6 (q. *C*-1'), 127.8 (t, *C*-3'', *C*-5''), 127.4 (t, C-2'', C-6''), 125.9 (t, C-4''), 111.8 (t, *C*-3', *C*-5'), 109.6 (q, *C*-8a), 101.1 (q, *C*-3a), 94.0 (t, *C*-7), 93.5 (s, OCH$_2$O-6), 93.4 (q, *C*-8b), 90.9 (t, *C*-5), 79.0 (t, *C*-1), 63.1 (p, NHO*C*H$_3$), 55.7 (p, H$_3$*C*OCH$_2$O-6), 55.5 (p, H$_3$*C*O-8), 54.8 (p, H$_3$*C*O-4'), 54.5 (t, *C*-3), 48.1 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{29}H_{31}NO_9Na$ $[M+Na]^+$ 560.1887, found 560.1897.

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-6-(((trifluoromethyl)sulfonyl)oxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-119)



(±)-119
$C_{28}H_{25}F_3O_{10}S$
MW: 610.55

To a solution of phenol **(±)-110** (179 mg, 374 µmol, 1.00 eq.) and *i*Pr$_2$EtN (108 µL, 636 µmol, 1.70 eq.) in CH_2Cl_2 (3.90 mL) at −10 °C was added trifluoromethanesulfonic anhydride (72.4 µL, 430 µmol, 1.15 eq.) dropwise over a period of 4 min. The mixture was stirred for 45 min and was then diluted with $NaHCO_3$ solution (aq., sat.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed successively with citric acid solution (10% in H_2O), H_2O and NaCl solution (aq., sat.), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified using flash chromatography (CH_2Cl_2/EtOAc 9:0 ⟶ 9:1) to give the desired triflate **(±)-119** as a pale-yellow foam (69.0 mg, 113 µmol) in 30% yield. In addition, phenol **(±)-110** was partially reisolated (73.0 mg, 153 µmol, 41%).

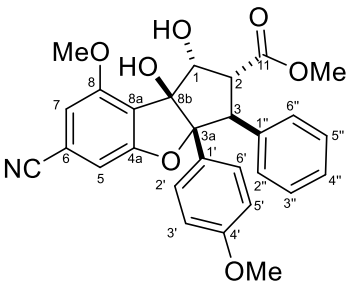
$\mathbf{R}_f$ = 0.45 (CH_2Cl_2/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.10 – 7.05 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.90 – 6.88 (m, 2H, *H*-2'', *H*-6''), 6.69 – 6.66 (m, 3H, *H*-5, *H*-3', *H*-5'), 6.44 (d, J = 2.0 Hz, 1H, *H*-7), 5.01 (dd, $\mathcal{J}$ = 6.2, 2.0 Hz, 1H, *H*-1), 4.35 (d, $\mathcal{J}$ = 14.3 Hz, 1H, *H*-3), 3.94 (dd, $\mathcal{J}$ = 14.1, 6.2 Hz, 1H, *H*-2), 3.93 (s, 3H, C*H*$_3$O-8), 3.71 (s, 3H, C*H*$_3$O-4'), 3.66 (s, 3H, C*H*$_3$O-11), 3.46 (d, $\mathcal{J}$ = 1.7 Hz, 1H, O*H*-8b), 1.92 (s, 1H, O*H*-1).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.7 (q, *C*-11), 160.4 (q, *C*-4a), 159.1 (q, *C*-4'), 157.4 (q, *C*-8), 152.3 (q, *C*-6), 136.4 (q, *C*-1''), 128.9 (t, C-2', C-6'), 128.0 (t, *C*-3'', *C*-5''), 127.9 (t, C-2'', C-6''), 126.9 (t, C-4''), 125.6 (q, C-1'), 120.4 – 117.2 (m, SO_2CF_3), 115.5 (q, *C*-8a), 113.1 (t, *C*-3', *C*-5'), 102.9 (q, *C*-3a), 98.8 (q, *C*-5), 98.3 (t, *C*-7), 93.5 (t, *C*-8b), 79.6 (t, *C*-1), 56.5 (p, H$_3$*C*O-8), 55.6 (t, *C*-3), 55.3 (p, H$_3$*C*O-4'), 52.3 (p, H$_3$*C*O-11), 50.5 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[66]

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-62)



(±)-62
$C_{28}H_{25}NO_7$
MW: 487.51

A mixture of the triflate **(±)-119** (69.0 mg, 113 µmol, 1.00 eq.), zinc cyanide (29.2 mg, 249 µmol, 2.20 eq.), 1,1′-bis(diphenylphosphino)ferrocene (13.2 mg, 23.7 µmol, 0.21 eq.) and tris(dibenzylideneacetone) dipalladium(0) (11.4 mg, 12.4 µmol, 0.11 eq.) in *N*-methylpyrrolidone (2.83 mL) was degassed for 5 min and heated to 100 °C for 20 h. The mixture was allowed to cool to rt and diluted with EtOAc (10.0 mL) and H_2O (10.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified using flash chromatography (CH_2Cl_2/EtOAc 4:0 ⟶ 4:1) to give the desired rocaglate **(±)-62** as a yellow foam (35.0 mg, 71.8 µmol) in 64% yield.

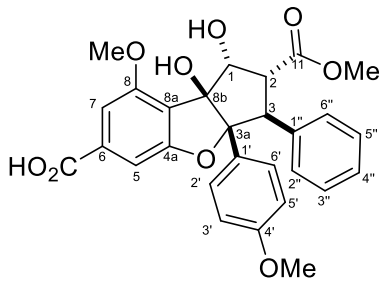
$\mathbf{R}_f$ = 0.41 (CH_2Cl_2/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.08 – 7.05 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 7.02 (s, 1H, *H*-5), 6.93-6.91 (m, 2H, *H*-2'', *H*-6''), 6.79 (s, 1H, *H*-7), 6.66 (d, J = 8.9 Hz, 2H, *H*-3', *H*-5'), 4.99 (d, J = 5.9 Hz, 1H, *H*-1), 4.36 (d, J = 14.2 Hz, 1H, *H*-3), 3.95 (dd, J = 14.3, 5.9 Hz, 1H, *H*-2), 3.93 (s, 3H, C*H*$_3$O-4'), 3.69 (s, 3H, C*H*$_3$O-8), 3.66 (s, 3H, C*H*$_3$O-11), 3.50 (bs, 1H, O*H*-8b), 2.07 (bs, 1H, O*H*-1).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.9 (q, *C*-11), 160.0 (q, *C*-4a), 159.1 (q, *C*-4'), 157.3 (q, *C*-8), 136.3 (q, *C*-1''), 128.8 (t, *C*-2', *C*-6'), 128.0 (t, *C*-3'', *C*-5''), 127.9 (t, *C*-2'', *C*-6''), 126.9 (t, *C*-4''), 125.6 (q. *C*-1'), 120.6 (q, N*C*-6), 118.6 (q, *C*-6), 115.4 (q, *C*-8a), 113.0 (t, *C*-3', *C*-5'), 109.0 (t, *C*-7), 107.8 (t, *C*-5), 102.0 (q, *C*-3a), 93.5 (q, *C*-8b), 79.6 (t, *C*-1), 56.5 (p, H$_3$*C*O-8), 55.8 (p, H$_3$*C*O-4'), 55.2 (t, *C*-3), 52.4 (p, H$_3$*C*O-11), 50.5 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[66]

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-2-(methoxycarbonyl)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-6-carboxylic acid ((±)-120)



(±)-120
$C_{28}H_{26}O_9$
MW: 506.51

A Schlenk finger was charged with triflate **(±)-119** (200 mg, 328 µmol, 1.00 eq.), 1,1′-bis(diphenylphosphino)ferrocene (36.3 mg, 65.5 µmol, 0.20 eq.), K_2CO_3 (226 mg, 1.64 mmol, 5.00 eq.) and $Pd(OAc)_2$ (7.35 mg, 32.8 µmol, 0.10 eq.) in DMF (1.09 mL). After degassing the solution for 15 min with argon, carbon monoxide was bubbled through the solution. Subsequently, the mixture was heated to 100 °C for 1 h. Then, the reaction was terminated by the addition of NaCl solution (aq., sat., 10.0 mL), acidified with HCl solution (1.00 M in H_2O) to pH 1-2 and extracted with EtOAc (3x 20.0 mL). The combined organic layers were washed with H_2O (10.0 mL) and aqueous NaCl solution (sat., 10.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (5.00 mL) and extracted with NaOH (0.25 M, aq., 3x 5.00 mL). The combined aqueous layers were washed with EtOAc (10.0 mL), then acidified to pH 1-2 with HCl (37 wt%, aq.) and extracted with EtOAc (3x 5.0 mL). After drying over $MgSO_4$ and concentration under reduced pressure, carboxylic acid **(±)-120** was obtained as a light-brown solid (120 mg, 237 µmol) in 72% yield.

$\mathbf{R}_f$ = 0.50 (CH_2Cl_2/MeOH = 9:1).

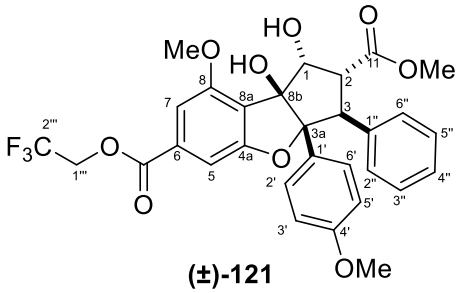
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.45 (d, J = 1.0 Hz, 1H, *H*-5), 7.26 (d, J = 1.0 Hz, 1H, *H*-7), 7.13 – 7.06 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.93 – 6.90 (m, 2H, *H*-2'', *H*-6''), 6.67 (d, J = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.07 (d, J = 6.3 Hz, 1H, *H*-1), 4.36 (d, J = 14.2 Hz, 1H, *H*-3), 3.98 (s, 3H, C*H*$_3$O-8), 3.96 (dd, J = 14.2, 6.3 Hz, 1H, *H*-2), 3.69 (s, 3H, C*H*$_3$O-4'), 3.66 (s, 3H, C*H*$_3$O-11).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.8 (q, *C*-11), 170.3 (q, HO$_2$*C*-C6), 160.0 (q, *C*-4a), 159.0 (q, *C*-4'), 156.6 (q, *C*-8), 136.6 (q, *C*-1''), 133.5 (q, *C*-6), 129.0 (t, *C*-2', *C*-6', *C*-3'', *C*-5''), 127.9 (t, *C*-2'', *C*-6''), 126.8 (t, *C*-4''), 126.0 (q, *C*-1'), 120.8 (q, *C*-8a), 113.0 (t, *C*-3', *C*-5'), 107.3 (t, *C*-5), 105.7 (t, *C*-7), 102.0 (q, *C*-3a), 93.6 (q, *C*-8b), 79.9 (t, *C*-1), 56.3 (p, H$_3$*C*O-8), 55.6 (t, *C*-3), 55.3 (p, H$_3$*C*O-4'), 52.3 (p, H$_3$*C*O-11), 50.5 (t, *C*-2).

HRMS (ESI$^-$) *m/z* calcd. for $C_{28}H_{25}O_9$ $[M–H]^-$ 505.1499, found 505.1508.

The analytical data are consistent with those reported in the literature.[66]

(±)-2-Methyl 6-(2,2,2-trifluoroethyl) (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-121)



(±)-121
$C_{30}H_{27}F_3O_9$
MW: 588.53

A solution of carboxylic acid **(±)-120** (10.0 mg, 19.7 µmol, 1.00 eq.) in anhydrous CH_2Cl_2 (1.00 mL) was treated with EDC·HCl (4.16 mg, 21.7 µmol, 1.10 eq.) and 4-DMAP (2.65 mg, 21.7 µmol, 1.10 eq.) at 0 °C. After 15 min, 2,2,2-trifluoroethanol (3.55 µL, 49.4 µmol, 2.50 eq.) was added and the reaction mixture was stirred for 16 h at rt. Then, the solution was diluted with CH_2Cl_2, washed with HCl solution (1.00 M in H_2O) and NaCl solution (aq., sat.) and dried over $MgSO_4$. After filtration and removal of the solvent, the residue was subjected to a silica gel chromatography column (petroleum ether/EtOAc 3:1 ⟶ 1:1) affording the desired ester **(±)-121** as a colorless solid (8.4 mg, 14.3 µmol) in 72% yield.

$\mathbf{R}_f$ = 0.24 (petroleum ether/EtOAc = 1:1).

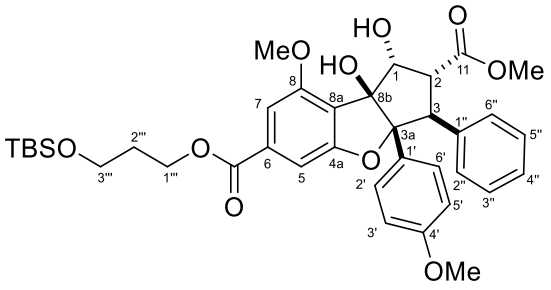
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.20 (d, $\mathcal{J}$ = 1.1 Hz, 1H, *H*-5), 7.11 (d, $\mathcal{J}$ = 1.1 Hz, 1H, *H*-7), 7.07 – 6.93 (m, 5H, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.57 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.48 (bs, O*H*-8b), 5.3 (d, $\mathcal{J}$ = 5.3 Hz, O*H*-1), 5.03 (q, $\mathcal{J}$ = 8.9 Hz, 2H, H-1'''), 4.89 (t, $\mathcal{J}$ = 4.9 Hz, 1H, *H*-1), 4.27 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 4.01 (dd, $\mathcal{J}$ = 14.0, 5.0 Hz, 1H, *H*-2), 3.82 (s, 3H, C*H*$_3$O-8), 3.58 (s, 3H, C*H*$_3$O-4'), 3.56 (s, 3H, C*H*$_3$O-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.2 (q, *C*-11), 164.1 (q, O$_2$*C*-C6), 159.8 (q, *C*-4a), 157.7 (q, *C*-8), 157.6 (q, *C*-4'), 138.1 (q, *C*-1''), 130.6 (q, *C*-6), 128.6 (t, C-2', C-6'), 128.2 (q, *C*-1'), 127.8 (t, *C*-3'', *C*-5''), 127.5 (t, C-2'', C-6''), 125.8 (t, C-4''), 123.6 (quartet, q, *C*-2'''), 121.8 (q, *C*-8a), 111.8 (t, *C*-3', *C*-5'), 104.7 (t, *C*-7), 104.0 (t, *C*-5), 101.7 (q, *C*-3a), 93.2 (q, *C*-8b), 78.7 (t, *C*-1), 60.4 (quartet, q, *C*-1''), 55.6 (p, H$_3$*C*O-8), 55.0 (t, *C*-3), 54.7 (p, H$_3$*C*O-4'), 51.4 (p, H$_3$*C*O-11), 51.3 (t, *C*-2).

^{19}F-NMR (DMSO-d_6, 376 MHz): δ [ppm] −72.5 (t, $\mathcal{J}$ = 9.0 Hz, 3*F*, *F*-2''').

HRMS (ESI$^+$) *m/z* calcd. for $C_{30}H_{27}F_3O_9Na$ $[M+Na]^+$ 611.1505, found 611.1500.

(±)-6-(3-((*tert*-Butyldimethylsilyl)oxy)propyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-122)



(±)-122
$C_{37}H_{46}O_{10}Si$
MW: 678.85

A solution of carboxylic acid **(±)-120** (10.0 mg, 19.7 µmol, 1.00 eq.) in anhydrous CH_2Cl_2 (1.00 mL), was treated with EDC·HCl (4.16 mg, 21.7 µmol, 1.10 eq.) and 4-DMAP (2.65 mg, 21.7 µmol, 1.10 eq.) at 0 °C. After 15 min, 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (9.40 mg, 49.4 µmol, 2.50 eq.) was added and the reaction mixture was stirred for 16 h at rt. Then, the solution was diluted with CH_2Cl_2, washed with HCl solution (1.00 M in H_2O) and NaCl solution (aq., sat.) and dried over $MgSO_4$. After filtration and removal of the solvent, the residue was subjected to a silica gel chromatography column (petroleum ether/EtOAc 4:1 ⟶ 1:1) affording ester **(±)-122** as a colorless solid (7.7 mg, 11.3 µmol) in 57% yield.

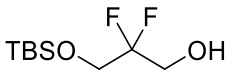
R_f = 0.39 (petroleum ether/EtOAc = 1:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.45 (d, J = 1.0 Hz, 1H, *H*-5), 7.25 (d, J = 1.0 Hz, 1H, *H*-7), 7.12 – 7.05 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.91 – 6.89 (m, 2H, *H*-2'', *H*-6''), 6.67 (d, J = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.05 (d, J = 6.3 Hz, 1H, *H*-1), 4.44 (t, J = 6.3 Hz, 2H, *H*-1'''), 4.35 (d, J = 14.2 Hz, 1H, *H*-3), 3.97 (s, 3H, C*H*$_3$O-8), 3.94 (dd, J = 14.2, 6.3 Hz, 1H, *H*-2), 3.80 (t, J = 6.1 Hz, 2H, *H*-3'''), 3.69 (s, 3H, C*H*$_3$O-4'), 3.66 (s, 3H, C*H*$_3$O-11), 2.00 (t, J = 6.3 Hz, 2H, *H*-2'''), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 0.08 (s, 6H, Si(C*H*$_3$)$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.7 (q, *C*-11), 166.0 (q, O$_2$*C*-C6), 159.9 (q, *C*-4a), 159.0 (q, *C*-4'), 156.5 (q, *C*-8), 136.7 (q, *C*-1''), 134.8 (q, *C*-6), 129.0 (t, *C*-3'', *C*-5''), 129.0 (t, *C*-2', *C*-6'/*C*-2'', *C*-6''),128.0 (t, *C*-2', *C*-6'/*C*-2'', *C*-6''), 126.8 (t, *C*-4''), 126.0 (q, *C*-1'), 119.9 (q, *C*-8a), 113.0 (t, *C*-3', *C*-5'), 106.6 (t, *C*-5), 105.2 (t, *C*-7), 101.9 (q, *C*-3a), 93.6 (q, *C*-8b), 79.9 (t, *C*-1), 62.6 (s, C-1'''), 59.6 (s, C-3'''), 56.3 (p, H$_3$*C*O-8), 55.5 (t, *C*-3), 55.3 (p, H$_3$*C*O-4'), 52.3 (p, H$_3$*C*O-11), 50.5 (t, *C*-2), 32.0 (s, *C*-2'''), 26.1 (p, SiC(*C*H$_3$)$_3$), 18.5 (q, Si*C*(CH$_3$)$_3$), −5.2 (p, Si(*C*H$_3$)$_2$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{37}H_{46}O_{10}SiNa$ $[M+Na]^+$ 701.2758, found 701.2738.

3-((*tert*-Butyldimethylsilyl)oxy)-2,2-difluoropropan-1-ol (E10)



E10
$C_9H_{20}F_2O_2Si$
MW: 226.34

A solution of 2,2-difluoropropane-1,3-diol (502 mg, 4.48 mmol, 1.00 eq.) in THF (9.00 mL) and treated with sodium hydride (90 wt%, 119 mg, 4.48 mmol, 1.00 eq.). After 45 min of stirring at rt, TBSCl (769 µL, 4.48 mmol, 1.00 eq.) was added dropwise and the mixture was stirred for addition 17 h. Then, the mixture was diluted with Et_2O, washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification by column chromatography (petroleum ether/EtOAc 7:1 ⟶ 3:1) the desired alcohol **E10** was obtained as a colorless oil (637 mg, 2.81 mmol) in 63% yield.

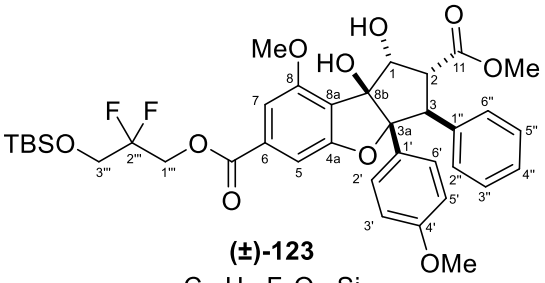
$\mathbf{R}_f$ = 0.61 (petroleum ether/EtOAc = 2:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 3.87 (t, J = 12.3 Hz, 2H, CH_2O), 3.86 (t, J = 12.8 Hz, 2H, CH_2O), 1.92 (bs, 1H, O*H*-1), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.10 (s, 6H, Si(CH_3)$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 121.1 (triplet, q, *C*F_2), 62.7 (triplet, s, *C*H_2), 62.1 (triplet, s, *C*H_2), 25.8 (p, SiC(*C*H_3)$_3$), 18.3 (q, Si*C*(CH$_3$)$_3$), −5.4 (p, Si(*C*H_3)$_2$).

The analytical data are consistent with those reported in the literature.[230]

(±)-6-(3-((*tert*-Butyldimethylsilyl)oxy)-2,2-difluoropropyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-123)



(±)-123
$C_{37}H_{44}F_2O_{10}Si$
MW: 714.83

A solution of carboxylic acid **(±)-120** (10.0 mg, 19.7 µmol, 1.00 eq.) in anhydrous CH_2Cl_2 (1.00 mL) was treated with EDC·HCl (4.16 mg, 21.7 µmol, 1.10 eq.) and 4-DMAP (2.65 mg, 21.7 µmol, 1.10 eq.) at 0 °C. After 15 min, alcohol **E10** (11.2 mg, 49.4 µmol, 2.50 eq.) was added and the reaction mixture was stirred for 16 h at rt. Then, the solution was diluted with CH_2Cl_2, washed with HCl solution (1.00 M in H_2O) and NaCl solution (aq., sat.) and dried over $MgSO_4$. After filtration and removal of the solvent, the residue was subjected to a silica gel chromatography column (petroleum ether/EtOAc 3:1 ⟶ 1:1) affording the desired ester **(±)-123** as a colorless solid (10.0 mg, 14.0 µmol) in 71% yield.

$\mathbf{R}_f$ = 0.35 (petroleum ether/EtOAc = 1:1).

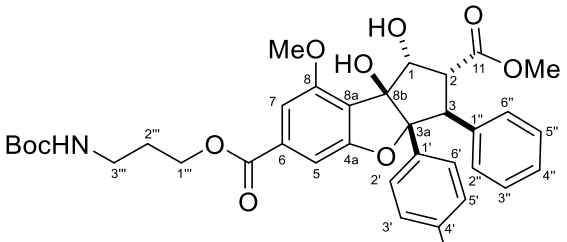
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.42 (d, J = 1.1 Hz, 1H, *H*-5), 7.26 (bs, 1H, *H*-7), 7.11 (d, J = 9.0 Hz, 2H, *H*-2', *H*-6'), 7.08 – 7.05 (m, 3H, *H*-3'', *H*-4'', *H*-5''), 6.93 – 6.90 (m, 2H, *H*-2'', *H*-6''), 6.68 (d, J = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.04 (d, J = 6.2 Hz, 1H, *H*-1), 4.62 (t, J = 12.7 Hz, 2H, *H*-1'''), 4.36 (d, J = 14.2 Hz, 1H,

H-3), 3.98 – 3.90 (m, 6H, *H*-2, C*H*$_3$O-8, *H*-3'''), 3.70 (s, 3H, C*H*$_3$O-4'), 3.66 (s, 3H, C*H*$_3$O-11), 3.62 (bs, 1H, O*H*-8b), 2.00 (bs, 1H, O*H*-1), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 0.12 (s, 6H, Si(C*H*$_3$)$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.8 (q, *C*-11), 165.0 (q, O$_2$*C*-C6), 160.0 (q, *C*-4a), 159.1 (q, *C*-4'), 156.5 (q, *C*-8), 136.6 (q, *C*-1''), 133.5 (q, *C*-6), 129.0 (t, *C*-3'', *C*-5''), 127.9 (t, *C*-2', *C*-6'/*C*-2'', *C*-6''), 127.9 (t, *C*-2', *C*-6'/*C*-2'', *C*-6''), 126.8 (t, *C*-4''), 125.9 (q, *C*-1'), 120.6 (q, *C*-8a), 120.1 (triplet, q, *C*-2'''), 113.0 (t, *C*-3', *C*-5'), 106.8 (t, *C*-5), 105.5 (t, *C*-7), 102.1 (q, *C*-3a), 93.6 (q, *C*-8b), 79.8 (t, *C*-1), 62.7 (triplet, s, C-1'''), 60.1 (triplet, s, C-3'''), 56.3 (p, H$_3$*C*O-8), 55.6 (t, *C*-3), 55.3 (p, H$_3$*C*O-4'), 52.3 (p, H$_3$*C*O-11), 50.5 (t, *C*-2), 25.8 (p, SiC(*C*H$_3$)$_3$), 18.3 (q, Si*C*(CH$_3$)$_3$), −5.4 (p, Si(*C*H$_3$)$_2$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{37}H_{46}O_{10}SiNa$ $[M+Na]^+$ 701.2758, found 701.2738.

(±)-6-(3-((*tert*-Butoxycarbonyl)amino)propyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*] benzofuran-2,6-dicarboxylate ((±)-124)



(±)-124
$C_{36}H_{41}NO_{11}$
MW: 663.72

A solution of carboxylic acid **(±)-120** (20.0 mg, 39.5 µmol, 1.00 eq.) in anhydrous CH_2Cl_2 (2.00 mL), was treated with EDC·HCl (8.3 mg, 43.4 µmol, 1.10 eq.) and 4-DMAP (8.3 mg, 43.4 µmol, 1.10 eq.) at 0 °C. After 15 min, *tert*-butyl (3-hydroxypropyl)carbamate (13.8 mg, 79.0 µmol, 2.00 eq.) was added and the reaction mixture was stirred for 16 h at rt. The resulting crude was washed with HCl solution (1.00 M in H_2O) and NaCl solution (aq., sat.) and dried over $MgSO_4$. After filtration and removal of the solvent, the residue was subjected to a silica gel chromatography column (petroleum ether/EtOAc 1:1) affording ester **(±)-124** as a colorless solid (22.0 mg, 33.1 µmol) in 84% yield.

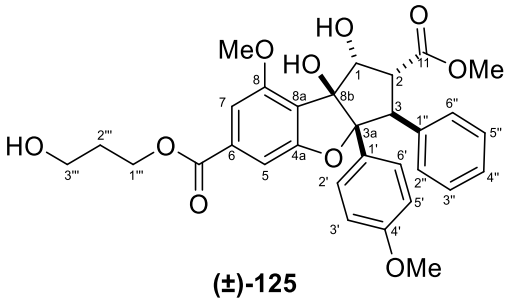
R$_f$ = 0.38 (petroleum ether/EtOAc = 1:2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.38 (d, $\mathcal{J}$ = 0.9 Hz, 1H, *H*-5), 7.24 (d, $\mathcal{J}$ = 0.9 Hz, 1H, *H*-7), 7.11 – 7.05 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.91 – 6.89 (m, 2H, *H*-2'', *H*-6''), 6.66 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-3', *H*-5'), 5.04 (d, $\mathcal{J}$ = 6.3 Hz, 1H, *H*-1), 4.80 (bs, 1H, N*H*), 4.40 (t, $\mathcal{J}$ = 6.1 Hz, 2H, *H*-1'''), 4.34 (d, $\mathcal{J}$ = 14.2 Hz, 1H, *H*-3), 3.96 (s, 3H, C*H*$_3$O-8), 3.94 (dd, $\mathcal{J}$ = 14.2, 6.4 Hz, 1H, *H*-2), 3.69 (s, 3H, C*H*$_3$O-4'), 3.65 (s, 3H, C*H*$_3$O-11), 3.33 – 3.26 (m, 2H, *H*-3'''), 2.00 (qi, $\mathcal{J}$ = 6.2 Hz, 2H, *H*-2'''), 1.45 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.7 (q, *C*-11), 166.1 (q, O$_2$*C*-C6), 159.9 (q, *C*-4a), 159.0 (q, *C*-4'), 156.6 (q, *C*-8), 156.1 (q, N*C*(O)), 136.7 (q, *C*-1''), 134.4 (q, *C*-6), 129.0 (t, *C*-3'', *C*-5''), 127.94 (t, *C*-2', *C*-6'/*C*-2'', *C*-6''), 127.91 (t, *C*-2', *C*-6'/*C*-2'', *C*-6''), 126.8 (t, *C*-4''), 126.0 (q, *C*-1'), 120.2 (q, *C*-8a), 112.9 (t, *C*-3', *C*-5'), 106.6 (t, *C*-5), 105.3 (t, *C*-7), 102.0 (q, *C*-3a), 93.6 (q, *C*-8b), 79.8 (t, *C*-1), 79.5 (q, C(*C*H$_3$)$_3$), 63.1 (s, C-1'''), 56.3 (p, H$_3$*C*O-8), 55.5 (t, *C*-3), 55.2 ((p, H$_3$*C*O-4'), 52.2 (p, H$_3$*C*O-11), 50.5 (t, *C*-2), 37.6 (s, C-3'''), 29.4 (s, C-2'''), 28.5 (p, OC(*C*H$_3$)$_3$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{36}H_{41}O_{11}Na$ $[M+Na]^+$ 686.2577, found 686.2574.

(±)-6-(3-Hydroxypropyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-125)



(±)-125
$C_{31}H_{32}O_{10}$
564.59

To an ice-cold solution of the TBS-protected alcohol **(±)-122** (7.7 mg, 11.3 µmol, 1.00 eq.) in anhydrous THF (1.13 mL), AcOH (6.5 µL, 113 µmol, 10.0 eq.) and tetra-*N*-butylammonium fluoride trihydrate (35.8 mg, 113 µmol, 10.0 eq.) were added sequentially. After stirring the mixture for 4 h at rt, the reaction was terminated by the addition of $NaHCO_3$ solution (aq., sat.) and diluted with CH_2Cl_2. The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was then purified by column chromatography (petroleum ether/EtOAc 1:1 ⟶ 1:3) to yield the desired product **(±)-125** as a colorless solid (5.6 mg, 9.92 µmol) in 87% yield.

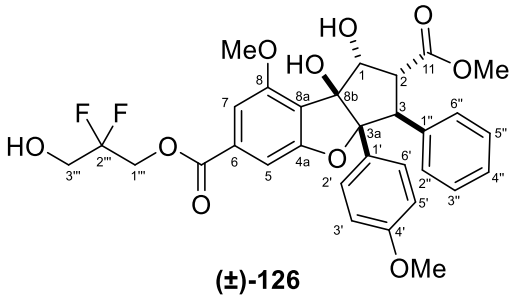
$\mathbf{R}_f$ = 0.21 (petroleum ether/EtOAc = 1:2).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.16 (d, $\mathcal{J}$ = 1.2 Hz, 1H, *H*-5), 7.08 (d, $\mathcal{J}$ = 1.1 Hz, 1H, *H*-7), 7.07 – 6.95 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.94 – 6.92 (m, 2H, *H*-2'', *H*-6''), 6.57 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.42 (bs, O*H*-8b), 5.36 (d, $\mathcal{J}$ = 4.1 Hz, O*H*-1), 4.70 (t, $\mathcal{J}$ = 4.3 Hz, 1H, *H*-1), 4.34 (td, $\mathcal{J}$ = 9.6, 1.2 Hz, 2H, *H*-1'''), 4.25 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 3.99 (dd, $\mathcal{J}$ = 14.0, 5.1 Hz, 1H, *H*-2), 3.80 (s, 3H, C*H*$_3$O-8), 3.59 – 3.54 (m, 2H, *H*-3'''), 3.58 (s, 3H, C*H*$_3$O-4'), 3.55 (s, 3H, C*H*$_3$O-11), 1.88 (qi, $\mathcal{J}$ = 6.3 Hz, 2H, *H*-2''').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.3 (q, *C*-11), 165.6 (q, O$_2$*C*-C6), 159.7 (q, *C*-4a), 157.52 (q, *C*-4'), 157.50 (q, *C*-8), 138.1 (q, *C*-1''), 132.7 (q, *C*-6), 128.6 (t, C-2', C-6'), 128.3 (q, *C*-1'), 127.8 (t, *C*-3'', *C*-5''), 127.5 (t, C-2'', C-6''), 125.8 (t, C-4''), 120.8 (q, *C*-8a), 111.8 (t, *C*-3', *C*-5'), 104.4 (t, *C*-7), 103.8 (t, *C*-5), 101.5 (q, *C*-3a), 93.2 (q, *C*-8b), 78.7 (t, *C*-1), 62.2 (s, C-1'''), 57.3 (s, C-3'''), 55.5 (p, H$_3$*C*O-8), 54.9 (t, *C*-3), 54.7 (p, H$_3$*C*O-4'), 51.4 (p, H$_3$*C*O-11), 51.2 (t, *C*-2), 31.6 (s, *C*-2''').

HRMS (ESI$^+$) *m/z* calcd. for $C_{31}H_{32}O_{10}Na$ $[M+Na]^+$ 587.1893, found 587.1885.

(±)-6-(2,2-Difluoro-3-hydroxypropyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo-furan-2,6-dicarboxylate ((±)-126)



(±)-126
$C_{31}H_{30}F_2O_{10}$
MW: 600.57

A solution of TBS-protected alcohol **(±)-123** (9.8 mg, 12.7 µmol, 1.00 eq.) in anhydrous THF (1.37 mL) was treated with AcOH (7.8 µL, 137 µmol, 10.0 eq.) and *n*$Bu_4NF{\cdot}3H_2O$ (43.2 mg, 137 µmol, 10.0 eq.) at 0 °C. After allowing the mixture to warm to rt, it was stirred 4 h. Then, the reaction was terminated by the addition of $NaHCO_3$ solution (aq., sat.) and diluted with CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was then purified by column chromatography (petroleum ether/EtOAc 1:1 ⟶ 1:3) to yield the desired ester **(±)-126** as a colorless solid (7.5 mg, 12.5 µmol) in 91% yield.

R$_f$ = 0.33 (CH_2Cl_2/MeOH = 95:5).

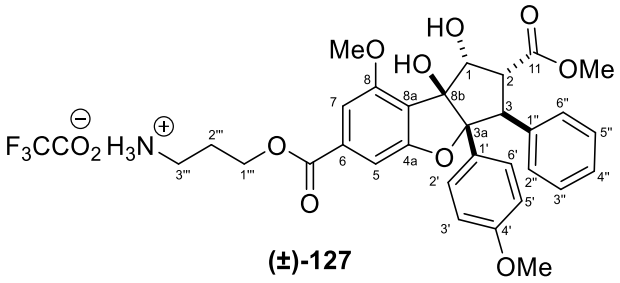
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.21 (d, $\mathcal{J}$ = 1.2 Hz, 1H, *H*-5), 7.10 (d, $\mathcal{J}$ = 1.1 Hz, 1H, *H*-7), 7.07 – 6.93 (m, 5H, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.57 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.74 (bs, 1H, O*H*-3'''), 5.46 (bs, O*H*-8b), 5.40 (d, $\mathcal{J}$ = 5.4 Hz, O*H*-1), 4.71 (t, $\mathcal{J}$ = 5.1 Hz, 1H, *H*-1), 4.63 (td, $\mathcal{J}$ = 20.4, 2.7 Hz, 2H, *H*-1'''), 4.27 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 4.01 (dd, $\mathcal{J}$ = 14.0, 5.1 Hz, 1H, *H*-2), 3.85 – 3.76 (m, 2H, *H*-3'''), 3.82 (s, 3H, C*H*$_3$O-8), 3.58 (s, 3H, C*H*$_3$O-4'), 3.56 (s, 3H, C*H*$_3$O-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.2 (q, *C*-11), 164.7 (q, O$_2$*C*-C6), 159.8 (q, *C*-4a), 157.6 (q, *C*-4'), 157.5 (q, *C*-8), 138.1 (q, *C*-1''), 131.4 (q, *C*-6), 128.6 (t, C-2', C-6'), 128.3 (q, *C*-1'), 127.8(t, *C*-3'', *C*-5''), 127.5 (t, C-2'', C-6''), 125.8 (t, C-4''), 121.4 (q, *C*-8a), 120.9 (triplet, q, *C*-2'''), 111.8 (t, *C*-3', *C*-5'), 104.6 (t, *C*-7), 104.0 (t, *C*-5), 101.6 (q, *C*-3a), 93.2 (q, *C*-8b), 78.7 (t, *C*-1), 61.6 (triplet, s, *C*-1'''), 60.4 (triplet, s, *C*-3'''), 55.6 (p, H$_3$*C*O-8), 55.0 (t, *C*-3), 54.7 (p, H$_3$*C*O-4'), 51.4 (p, H$_3$*C*O-11), 51.3 (t, *C*-2).

^{19}F-NMR (DMSO-d_6, 376 MHz): δ [ppm] −114.3 (qi, $\mathcal{J}$ = 13.6 Hz, 2F, *F*-2''').

HRMS (ESI$^+$) *m/z* calcd. for $C_{31}H_{30}F_2O_{10}Na$ $[M+Na]^+$ 623.1705, found 623.1717.

(±)-3-(((1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-2-(methoxycarbonyl)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-6-carbonyl)oxy)propan-1-aminium 2,2,2-trifluoroacetate ((±)-127)



(±)-127
$C_{33}H_{34}F_3NO_{11}$
MW: 677.63

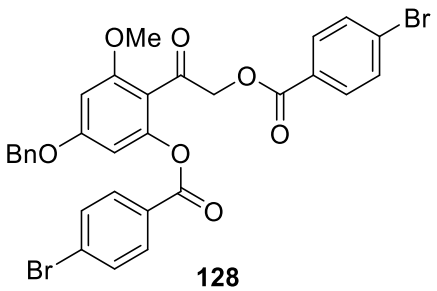
Trifluoroacetic acid (22.3 µL, 289 µmol, 10.0 eq.) was added dropwise into a solution of the Boc-protected amine **(±)-124** (19.2 mg, 28.9 µmol, 1.00 eq.) in anhydrous CH_2Cl_2 (1.00 mL) in an ice bath. The reaction mixture was then stirred at rt for 18 h and was subsequently poured into a large amount of ether (10.0 mL). The precipitate was filtered, washed with ether several times and then dried under vacuum to obtain the desired salt **(±)-127** as a yellowish solid (8.9 mg, 13.1 µmol) in 45% yield.

^{1}H-NMR (DMSO-d_6, 600 MHz): δ [ppm] 7.81 (bs, 3H, N*H*$_3$), 7.23 (d, J = 1.1 Hz, 1H, *H*-5), 7.09 (d, J = 1.0 Hz, 1H, *H*-7), 7.05 (t, J = 7.5 Hz, 2H, *H*-3'', *H*-5''), 7.01 (d, J = 9.0 Hz, 2H, *H*-2', *H*-6'), 6.98 (t, J = 7.3 Hz, 1H, *H*-4''), 6.93 (d, J = 7.6 Hz, 2H, *H*-2'', *H*-6''), 6.57 (dt, J = 9.0, 2.7 Hz, 2H, *H*-3', *H*-5'), 5.43 (s, O*H*-8b), 5.31 (d, J = 5.4 Hz, O*H*-1), 4.72 (t, J = 5.2 Hz, 1H, *H*-1), 4.35 (tq, J = 17.8, 5.9 Hz, 2H, *H*-1'''), 4.25 (d, J = 14.0 Hz, 1H, *H*-3), 4.01 (dd, J = 14.0, 5.1 Hz, 1H, *H*-2), 3.80 (s, 3H, C*H*$_3$O-8), 3.58 (s, 3H, C*H*$_3$O-4'), 3.56 (s, 3H, C*H*$_3$O-11), 3.01 (bs, 2H, *H*-3'''), 2.04 (qi, J = 6.7 Hz, 2H, *H*-2''').

^{13}C-NMR (DMSO-d_6, 150 MHz, peaks of TFA not included): δ [ppm] 170.3 (q, *C*-11), 165.5 (q, O$_2$*C*-C6), 159.7 (q, *C*-4a), 157.6 (q, *C*-4'), 157.5 (q, *C*-8), 138.1 (q, *C*-1''), 132.4 (q, *C*-6), 128.6 (t, C-2', C-6'), 128.3 (q, *C*-1'), 127.8 (t, *C*-3'', *C*-5''), 127.5 (t, C-2'', C-6''), 125.8 (t, C-4''), 121.0 (q, *C*-8a), 111.8 (t, *C*-3', *C*-5'), 104.5 (t, *C*-7), 103.9 (t, *C*-5), 101.6 (q, *C*-3a), 93.2 (q, *C*-8b), 78.7 (t, *C*-1), 62.4 (s, C-1'''), 55.6 (p, H$_3$*C*O-8), 55.0 (t, *C*-3), 54.8 (p, H$_3$*C*O-4'), 51.4 (p, H$_3$*C*O-11), 51.2 (t, *C*-2), 36.4 (s, C-3'''), 26.4 (s, *C*-2''').

HRMS (ESI$^+$) *m/z* calcd. for $C_{31}H_{34}NO_8$ [M]$^+$ 564.2234, found 564.2247.

2-(4-(Benzyloxy)-2-((4-bromobenzoyl)oxy)-6-methoxyphenyl)-2-oxoethyl 4-bromobenzoate (128)



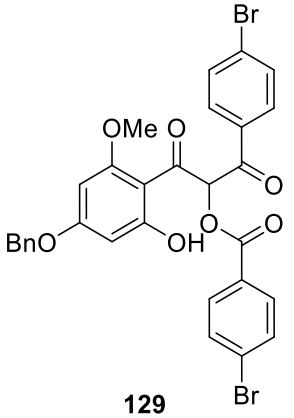
128
$C_{30}H_{22}Br_2O_7$
MW: 654.31

A solution of the α-hydroxy ketone **106** (3.07 g, 10.6 mmol, 1.00 eq.) in CH_2Cl_2 (35.5 mL) was treated with 4-DMAP (65.0 mg, 532 µmol, 5 mol%) and triethylamine (4.45 mL, 31.9 mmol, 3.00 eq.). The

mixture was cooled to 0 °C and 4-bromobenzoyl chloride (4.67 g, 21.3 mmol, 2.00 eq.) was added and stirred at rt for 3.5 h. The solution was terminated by the addition of HCl (1.00 M in H_2O) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired bisbenzoate **128** was obtained as a yellow foam (6.97 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.50 (petroleum ether/EtOAc 2:1).

1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)-3-(4-bromophenyl)-1,3-dioxopropan-2-yl 4-bromobenzoate (129)



129

$C_{30}H_{22}Br_2O_7$

MW: 654.31

A solution of crude bisbenzoate **128** (6.97 g, 10.7 mmol, 1.00 eq.) in THF (59.2 mL) was cooled to −20 °C and treated with LiHMDS solution (1.00 M in THF, 32.0 mL, 32.0 mmol, 3.00 eq.). The mixture was stirred at −20 °C for 30 min. Then, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.) and warmed to rt. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was suspended in EtOH and heated under refluxing conditions for 15 min. After cooling to rt, the suspension was filtered and the solid was washed with cold EtOH. The desired phenol **129** was obtained as a pale-yellow solid (4.93 g, 7.54 mmol) in 71% yield.

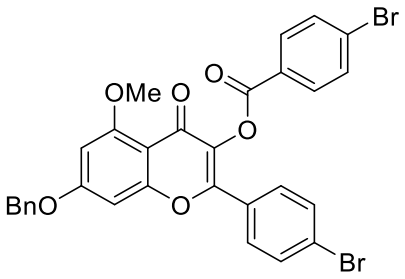
$\mathbf{R}_f$ = 0.50 (petroleum ether/EtOAc 2:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.14 (bs, 1H, O*H*), 7.96 (d, J = 8.6 Hz, 2H, 2x Ar*H*), 7.89 (d, J = 8.6 Hz, 2H, 2x Ar*H*), 7.67 (d, J = 8.6 Hz, 2H, 2x Ar*H*), 7.59 (d, J = 8.6 Hz, 2H, 2x Ar*H*), 7.40 – 7.34 (m, 6H, 5x Ar*H*, C*H*O), 6.20 (d, J = 2.1 Hz, 1H, Ar*H*), 5.93 (d, J = 2.1 Hz, 1H, Ar*H*), 5.06 (s, 2H, OCH_2Ph), 3.35 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.3 (q, *C*=O), 190.0 (q, *C*=O), 167.9 (q, *C*(=O)O), 166.4 (q, Ar*C*), 164.9 (q, Ar*C*), 161.5 (q, Ar*C*), 135.7 (q, Ar*C*), 133.5 (q, Ar*C*), 132.6 (t, 2x Ar*C*), 132.1 (t, 2x Ar*C*), 131.8 (t, 2x Ar*C*), 130.3 (t, 2x Ar*C*), 129.6 (q, Ar*C*), 129.3 (q, Ar*C*), 128.9 (t, 2x Ar*C*), 128.6 (t, Ar*C*H), 127.8 (t, 2x Ar*C*), 127.7 (q, Ar*C*), 104.6 (t, Ar*C*H), 95.3 (t, Ar*C*H), 91.9 (t, Ar*C*H), 76.9 (t, H*C*O), 70.6 (s, O*C*H_2Ph), 55.6 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[66]

7-(Benzyloxy)-2-(4-bromophenyl)-5-methoxy-4-oxo-4*H*-chromen-3-yl 4-bromobenzoate (130)



130
$C_{30}H_{20}Br_2O_6$
MW: 636.29

A suspension of crude phenol **129** (4.42 g, 6.76 mmol, 1.00 eq.) in AcOH (92.0 mL) was treated with H_2SO_4 (96 wt%, 2.09 mL, 35.4 mmol, 5.24 eq.) and stirred at 50 °C for 20 h. The reaction mixture was poured into ice-cold H_2O, the yellow suspension was filtered and the precipitate was washed with H_2O. The wet solid was suspended in a minimal amount of EtOH and heated under refluxing conditions for 45 min. After cooling to rt, the mixture was filtered, the precipitate was washed with cold EtOH and dried under reduced pressure to give a mixture of **130** and ~40% of the de-benzylated flavonol ester. The solid was dissolved in DMF (65.0 mL) and treated with BnBr (807 µL, 6.76 mmol, 1.00 eq.) and K_2CO_3 (1.87 g, 13.5 mmol, 2.00 eq.), stirred at rt for 2.5 h and then diluted with CH_2Cl_2 (100 mL) and NaCl solution (aq., sat., 100 mL). The phases were separated and the organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was suspended in a minimal amount of EtOH and heated to reflux for 1 h, cooled to rt and filtered. After washing with cold EtOH and drying under reduced pressure, the desired 3-benzyloxyflavonate **130** was obtained as a yellow solid (3.25 g, 5.11 mmol) in 76% yield.

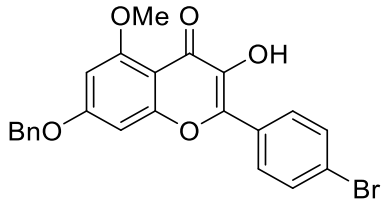
$\mathbf{R}_f$ = 0.60 (petroleum ether/EtOAc 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.03 (d, J = 8.2 Hz, 2H, 2x Ar*H*), 7.74 (d, J = 8.3 Hz, 2H, 2x Ar*H*), 7.63 (d, J = 8.4 Hz, 2H, 2x Ar*H*), 7.58 (d, J = 8.3 Hz, 2H, 2x Ar*H*), 7.45 – 7.38 (m, 5H, 5x Ar*H*), 6.63 (s, 1H, Ar*H*), 6.47 (s, 1H, Ar*H*), 5.16 (s, 2H, OCH_2Ph), 3.91 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.4 (q, *C*=O), 163.9 (q, Ar*C*), 163.5 (q, O*C*=O), 161.5 (q, Ar*C*), 159.3 (q, Ar*C*), 152.7 (q, *C*=C-O), 135.6 (q, Ar*C*), 134.8 (q, C=*C*-O), 132.14 (t, 4x Ar*C*), 132.09 (t, 2x Ar*C*), 129.6 (t, 2x Ar*C*), 129.2 (q, Ar*C*), 129.0 (t, 2x Ar*C*), 128.9 (q, Ar*C*), 128.7 (t, Ar*C*H), 127.81 (q, Ar*C*), 127.76 (t, 2x Ar*C*), 125.8 (q, Ar*C*), 109.1 (q, Ar*C*), 97.0 (t, Ar*C*H), 93.7 (t, Ar*C*H), 70.8 (s, O*C*H_2Ph), 56.5 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[66]

7-(Benzyloxy)-2-(4-bromophenyl)-3-hydroxy-5-methoxy-4*H*-chromen-4-one (131)



131
$C_{23}H_{17}BrO_5$
MW: 453.29

A suspension of the benzoate **130** (1.00 g, 1.57 mmol, 1.00 eq.) in EtOH (20.8 mL) was treated with NaOH solution (5 wt% in H_2O, 2.39 mL, 3.14 mmol, 2.00 eq.). The yellowish suspension was stirred at 80 °C for 1.75 h. The reaction mixture was allowed to cool to rt and was neutralized with HCl (1.00 M in H_2O, 3.30 mL, 3.30 mmol, 2.10 eq.). The resulting suspension was filtered on a BÜCHNER funnel and the precipitate was washed with a small amount of cold ethanol. The solid was dried under reduced pressure to constant weight to give the desired 3-hydroxyflavone **131** as a yellowish solid (634 mg, 1.40 mmol) in 89% yield.

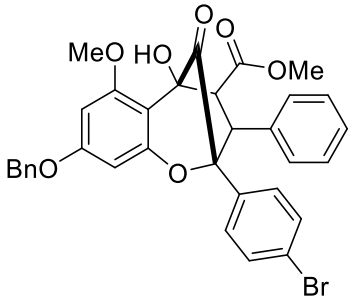
$\mathbf{R}_f$ = 0.48 (petroleum ether/EtOAc 2:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.09 (d, J = 8.6 Hz, 2H, 2x Ar*H*), 7.64 (d, J = 8.6 Hz, 2H, 2x Ar*H*), 7.49 – 7.37 (m, 5H, 5x Ar*H*), 6.65 (d, J = 1.7 Hz, 1H, Ar*H*), 6.45 (d, J = 1.7 Hz, 1H, Ar*H*), 5.16 (s, 2H, OC*H*$_2$Ph), 3.98 (s, 3H, OC*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.1 (q, *C*=O), 163.9 (q, Ar*C*), 160.8 (q, Ar*C*), 159.0 (q, Ar*C*), 141.0 (q, *C*=COH), 138.6 (q, *C*OH), 135.6 (q, Ar*C*), 131.9 (t, 2x Ar*C*), 130.2 (q, Ar*C*), 129.0 (t, 2x Ar*C*), 128.8 (t, 2x Ar*C*), 128.7 (t, Ar*C*H), 127.8 (t, 2x Ar*C*), 124.1 (q, Ar*C*), 106.5 (q, Ar*C*), 96.5 (t, Ar*C*H), 93.5 (t, Ar*C*H), 70.8 (s, O*C*H$_2$Ph), 56.5 (p, O*C*H$_3$).

The analytical data are consistent with those reported in the literature.[66]

(±)-Methyl (3*S*,4*S*,5*R*)-8-(benzyloxy)-2-(4-bromophenyl)-5-hydroxy-6-methoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E11)



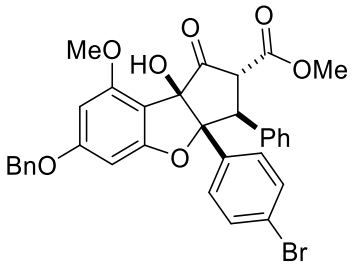
E11
$C_{33}H_{27}BrO_7$
MW: 615.48

Methyl cinnamate (3.20 g, 19.7 mmol, 14.2 eq.) was added to a solution of flavonol **131** (629 mg, 1.39 mmol, 1.00 eq.) in dry chloroform (28.3 mL) and freshly distilled 2,2,2-trifluoroethanol (11.3 mL). The reaction mixture was degassed for 30 min, then cooled to –5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (24 h). Subsequently, the solvent was removed

under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 5.5:1 ⟶ 1:1). Product **E11** was obtained as a mixture of isomers as a yellowish foam (629 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.23 – 0.60 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-3a-(4-Bromophenyl)-8b-hydroxy-8-methoxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E12)

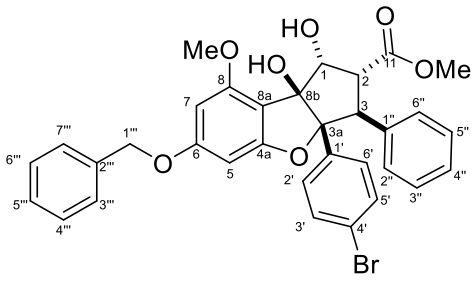


E12
$C_{33}H_{27}BrO_7$
MW: 615.48

Cycloadduct **E11** (629 mg, 1.02 mmol, 1.00 eq.) was dissolved in MeOH (40.9 mL). Then NaOMe solution (25 wt% in MeOH, 799 µL, 3.37 mmol, 3.30 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E12** was obtained as a mixture of isomers as a yellow, glassy foam (629 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.25 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(Benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-8-methoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-132)



(±)-132
$C_{33}H_{29}BrO_7$
MW: 617.49

A mixture of $(CH_3)_4N(OAc)_3BH$ (1.73 g, 6.56 mmol, 6.42 eq.) and freshly distilled AcOH (612 µL, 10.6 mmol, 10.4 eq.) in MeCN (9.00 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E12** (629 mg, 1.02 mmol, 1.00 eq.) in MeCN (6.00 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was

extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (petroleum ether/EtOAc 5:1 ⟶ 1:1) was then performed to obtain the racemic *endo*-product **(±)-132** as a pale-yellow solid (293 mg, 483 µmol) in a yield of 35% over 3 steps.

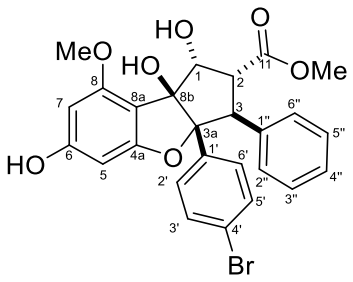
$\mathbf{R}_f$ = 0.52 (petroleum ether/EtOAc 1:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.47 – 7.34 (m, 5H, *H*-3''', *H*-4''', *H*-5''', *H*-6''', *H*-7'''), 7.26 (d, J = 8.7 Hz, *H*-3', *H*-5'), 7.08 – 7.05 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.89 – 6.86 (m, 2H, *H*-2'', *H*-6''), 6.36 (d, J = 1.9 Hz, 1H, *H*-5), 6.22 (d, J = 1.9 Hz, 1H, *H*-7), 5.09 (s, 2H, *H*-1'''), 5.01 (dd, J = 6.5, 1.4 Hz, 1H, *H*-1), 4.35 (d, J = 14.2 Hz, 1H, *H*-3), 3.81 (dd, J = 14.2, 6.5 Hz, 1H, *H*-2), 3.86 (s, 3H, C*H*$_3$O-8), 3.66 (s, 3H, C*H*$_3$O-11), 3.59 (s, 1H, O*H*-8b), 1.85 (s, 1H, O*H*-1).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 170.5 (q, *C*-11), 163.5 (q, *C*-6), 160.8 (q, *C*-4a), 157.1 (q, *C*-8), 136.6 (q, *C*-2'''), 136.5 (q, *C*-1''), 133.9 (q, *C*-1'), 130.4 (t, *C*-3', *C*-5'), 129.6 (t, *C*-2', *C*-6'), 128.9 (t, *C*-4''', *C*-6'''), 128.4 (t, *C*-5'''), 128.0 (t, *C*-3'', *C*-5''), 127.8 (t, *C*-2'', *C*-6''), 127.7 (t, *C*-3''', *C*-7'''), 126.9 (t, *C*-4''), 121.8 (q. *C*-4'), 107.6 (q, *C*-8a), 101.8 (q, *C*-3a), 93.9 (q, *C*-8b), 93.6 (t, *C*-7), 90.6 (t, *C*-5), 79.7 (t, *C*-1), 70.7 (s, *C*-1'''), 55.9 (p, H$_3$*C*O-8), 55.1 (t, *C*-3), 52.2 (p, H$_3$*C*O-11), 50.5 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[66]

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,6,8b-trihydroxy-8-methoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-133)



(±)-133
$C_{26}H_{23}BrO_7$
MW: 527.37

Palladium on carbon (10 wt%, 78.2 mg, 73.5 µmol, 20 mol%) was added to a solution of *endo*-benzyl ether **(±)-132** (227 mg, 368 µmol, 1.00 eq.) in dry THF (7.35 mL) under an argon atmosphere. The atmosphere was replaced by hydrogen and an additional balloon of hydrogen was placed on the flask. The reaction mixture was stirred for 50 min at rt and then filtered over Celite®. The filtrate was concentrated to dryness and gave the desired phenol **(±)-133** as a colorless solid (177 mg, 336 µmol) in 91% yield.

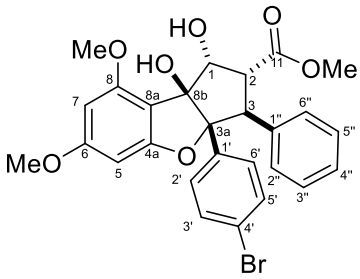
$\mathbf{R}_f$ = 0.27 (CH_2Cl_2/EtOAc 19:1).

^{1}H-NMR (acetone-d_6, 400 MHz): δ [ppm] 7.22 (dt, J = 9.1, 2.2 Hz, 2H, *H*-3', *H*-5'), 7.14 (dt, J = 9.1, 2.2 Hz, 2H, *H*-2', *H*-6'), 7.07 – 6.95 (m, 5H, *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.17 (d, J = 1.8 Hz, *H*-5), 6.10 (d, J = 1.8 Hz, *H*-7), 4.90 (d, J = 5.8 Hz, *H*-1), 4.37 (d, J = 14.1 Hz, *H*-3), 4.26 (bs, 1H, O*H*-8b), 4.01 (dd, J = 14.1, 6.1 Hz, 1H, *H*-2), 3.80 (s, 3H, C*H*$_3$O-8), 3.56 (s, 3H, C*H*$_3$O-11).

^{13}C-NMR (acetone-d_6, 100 MHz): δ [ppm] 170.9 (q, *C*-11), 162.4 (q, *C*-6), 161.6 (q, *C*-4a), 158.7 (q, *C*-8), 138.9 (q, *C*-1''), 136.9 (q, *C*-1'), 130.9 (t, *C*-3', *C*-5'), 130.3 (t, *C*-2', *C*-6'), 128.7 (t, *C*-3'', *C*-5''), 128.4 (t, *C*-2'', *C*-6''), 127.0 (t, *C*-4''), 121.0 (q. *C*-4'), 107.6 (q, *C*-8a), 102.4 (q, *C*-3a), 94.6 (q, *C*-8b), 93.4 (t, *C*-7), 91.7 (t, *C*-5), 80.6 (t, *C*-1), 55.8 (p, H$_3$*C*O-8), 55.7 (t, *C*-3), 51.70 (p, H$_3$*C*O-11), 51.67 (t, *C*-2).

HRMS (ESI$^-$) *m/z* calcd. for $C_{26}H_{22}BrO_7$ [M-H]$^-$ 525.0549, found 525.0562.

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-134)



(±)-134
$C_{27}H_{25}BrO_7$
MW: 541.39

A solution of the phenol **(±)-133** (166 mg, 315 µmol, 1.00 eq.) in toluene (10.5 mL) and MeOH (10.5 mL) was treated with trimethylsilyldiazomethane (2.00 M in Et_2O, 1.57 mL, 3.15 mmol, 10.0 eq.) and stirred for 4 h at rt. The solvents were removed under reduced pressure. The residue was purified using silica gel chromatography (petroleum ether/EtOAc 2:1) to give the desired rocaglate **(±)-134** as a colorless foam (135 mg, 249 µmol) in 79% yield.

$\mathbf{R}_f$ = 0.41 (petroleum ether/EtOAc 1:1).

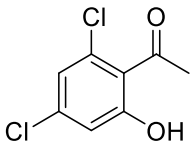
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.20 (dt, J = 9.4, 2.2 Hz, 2H, *H*-3', *H*-5'), 7.08 – 7.04 (m, 4H, *H*-2', *H*-6', *H*-2'', *H*-6''), 7.01 – 6.97 (m, 1H, *H*-4''), 6.93 (d, J = 7.4 Hz, 2H, *H*-3'', *H*-5''), 6.28 (d, J = 2.0 Hz, 1H, *H*-5), 6.11 (d, J = 2.0 Hz, 1H, *H*-7), 5.25 (s, 1H, O*H*-8b), 5.12 (d, J = 4.9 Hz, 1H, O*H*-1), 4.65 (t, J = 5.1 Hz, 1H, *H*-1), 4.24 (d, J = 14.0 Hz, 1H, *H*-3), 4.00 (dd, J = 14.0, 5.3 Hz, 1H, *H*-2), 3.78 (s, 3H, C*H*$_3$O-6), 3.72 (s, 3H, C*H*$_3$O-8), 3.56 (s, 3H, C*H*$_3$O-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.3 (q, *C*-11), 162.7 (q, *C*-6), 160.4 (q, *C*-4a), 157.8 (q, *C*-8), 138.0 (q, *C*-1''), 136.3 (q, *C*-1'), 129.8 (t, *C*-3', *C*-5'), 129.2 (t, *C*-2', *C*-6'), 127.7 (t, *C*-3'', *C*-5''), 127.6 (t, *C*-2'', *C*-6''), 126.0 (t, *C*-4''), 119.6 (q. *C*-4'), 107.8 (q, *C*-8a), 101.2 (q, *C*-3a), 93.4 (q, *C*-8b), 91.9 (t, *C*-7), 88.3 (t, *C*-5), 78.7 (t, *C*-1), 55.5 (p, H$_3$*C*O-6), 55.3 (p, H$_3$*C*O-8), 54.7 (t, *C*-3), 51.3 (p, H$_3$*C*O-11), 51.1 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{25}O_7BrNa$ [M+Na]$^+$ 563.0681, found 563.0680.

The analytical data are consistent with those reported in the literature.[58]

1-(2,4-Dichloro-6-hydroxyphenyl)ethan-1-one (137)



137
$C_8H_6Cl_2O_2$
MW: 205.03

To a solution of the 3,5-dichlorophenol (**135**) (10.0 g, 61.3 mmol, 1.00 eq.) and dry pyridine (7.43 mL, 92.0 mmol, 1.50 eq.) in anhydrous CH_2Cl_2 (81.8 mL) was slowly added acetyl chloride (5.70 mL, 79.8 mmol, 1.30 eq.) and the reaction was stirred at rt for 30 min. Then, $NaHCO_3$ solution (aq., sat.) was added and the mixture was extracted with CH_2Cl_2 (3x), washed with H_2O, dried over $MgSO_4$, filtered and concentrated to yield 3,5-dichlorophenyl acetate which was used without further purification. To the compound was added $AlCl_3$ (10.6 g, 79.8 mmol, 1.30 eq.) and the mixture was heated to 150 °C with stirring for 10 min. The reaction mixture was allowed to cool to rt and dissolved in EtOAc before careful terminating with H_2O. After phase separation, the aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish the crude product as an oil that crystallized on standing. After recrystallization from EtOH, acetophenone **137** was obtained as a light brown solid (7.89 g, 38.5 mmol) in 63% yield.

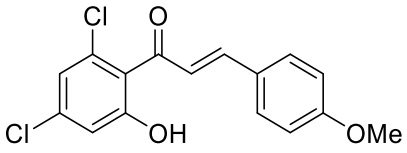
$\mathbf{R}_f$ = 0.70 (CH_2Cl_2/EtOAc 85:15).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 12.76 (s, 1H, O*H*), 6.98 (d, J = 2.1 Hz, 1H, Ar*H*), 6.94 (d, J = 2.1 Hz, 1H, Ar*H*), 2.84 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.6 (q, *C*=O), 164.6 (q, Ar*C*), 140.8 (q, Ar*C*), 136.1 (q, Ar*C*), 122.6 (t, Ar*C*H), 118.4 (q, Ar*C*), 117.9 (t, Ar*C*H), 33.8 (p, *C*H_3).

The analytical data are consistent with those reported in the literature.[231]

(*E*)-1-(2,4-Dichloro-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (139)



139
$C_{16}H_{12}Cl_2O_3$
MW: 323.17

Acetophenone **137** (500 mg, 2.44 mmol, 1.00 eq.) was added to a solution of NaOEt (498 mg, 7.32 mmol, 3.00 eq.) in EtOH (8.41 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (296 µL, 2.44 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired chalcone **139** was obtained as a yellow solid (744 mg, 2.30 mmol) in 94% yield.

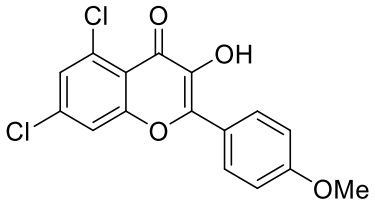
$\mathbf{R}_f$ = 0.43 (petroleum ether/EtOAc 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 11.58 (s, 1H, O*H*), 7.82 (d, J = 15.5 Hz, 1H, C(O)CH=C*H*), 7.60 (d, J = 8.7 Hz, 2H, 2x Ar*H*), 7.51 (d, J = 15.4 Hz, 1H, C(O)C*H*), 7.01 – 6.94 (m, 4H, 4x Ar*H*), 3.87 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.6 (q, *C*=O), 162.8 (q, Ar*C*), 162.4 (q, Ar*C*), 144.9 (t, C(O)CH=*C*H), 139.7 (q, Ar*C*), 134.7 (q, Ar*C*), 130.9 (t, 2x Ar*C*H), 127.4 (q, Ar*C*), 123.6 (t, C(O)*C*H), 122.3 (t, Ar*C*H), 120.3 (q, Ar*C*), 117.3 (t, Ar*C*H), 114.7 (t, 2x Ar*C*H), 55.6 (p, O*C*H_3).

The analytical data are consistent with those reported in the literature.[231]

5,7-Dichloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (141)



141
$C_{16}H_{10}Cl_2O_4$
MW: 337.15

To a suspension of chalcone **139** (646 mg, 2.00 mmol, 1.00 eq.) in MeOH (17.2 mL), NaOH (3.00 M, aq., 2.58 mL, 7.74 mmol, 3.87 eq.) was added and cooled to 0 °C. H_2O_2 (30 wt% in H_2O, 652 µL, 6.40 mmol, 3.20 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 20 h. Then, HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate. The suspension was then extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOAc to give the desired product **141** as a pale-yellowish solid (172 mg, 510 µmol) in 26% yield.

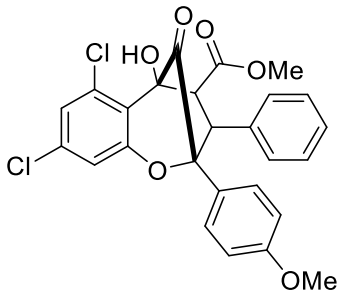
R$_f$ = 0.42 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.18 (d, J = 9.0 Hz, 2H, 2x Ar*H*), 7.53 (d, J = 1.8 Hz, 1H, Ar*H*), 7.40 (d, J = 1.8 Hz, 1H, Ar*H*), 7.17 (s, 1H, O*H*), 7.05 (d, J = 9.0 Hz, 2H, 2x Ar*H*), 3.90 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 171.7 (q, *C*=O), 161.5 (q, Ar*C*), 156.6 (q, Ar*C*), 144.2 (q, *C*=COH), 138.6 (q, Ar*C*), 138.2 (q, *C*OH), 134.5 (q, Ar*C*), 129.5 (t, 2x Ar*C*H), 127.6 (t, Ar*C*H), 122.7 (q, Ar*C*), 117.6 (t, Ar*C*H), 116.6 (q, Ar*C*), 114.4 (t, 2x Ar*C*H), 55.6 (p, O*C*H_3).

HRMS (EI) *m/z* calcd. for $C_{16}H_{10}Cl_2O_4$ $[M]^+$ 335.9956, found 335.9971.

(±)-Methyl (3*S*,4*S*,5*R*)-6,8-dichloro-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E13)

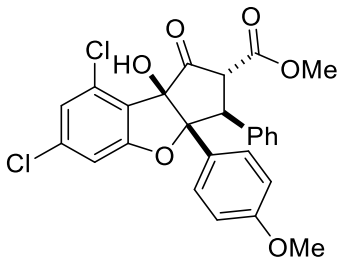


E13
$C_{26}H_{20}Cl_2O_6$
MW: 499.34

Methyl cinnamate (1.14 g, 7.03 mmol, 14.2 eq.) was added to a solution of flavonol **141** (167 mg, 495 µmol, 1.00 eq.) in dry chloroform (9.71 mL) and freshly distilled 2,2,2-trifluoroethanol (4.13 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 9:1 → 1:1). Product **E13** was obtained as a mixture of isomers as a yellowish solid (185 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.18 – 0.61 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-6,8-dichloro-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E14)

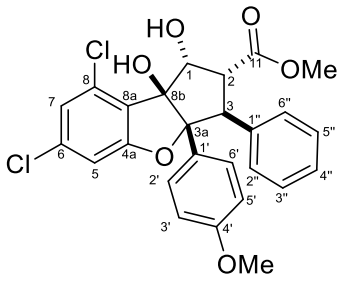


E14
$C_{26}H_{20}Cl_2O_6$
MW: 499.34

Cycloadduct **E13** (185 mg, 370 µmol, 1.00 eq.) was dissolved in MeOH (13.7 mL). Then, NaOMe solution (200 µL, 25 wt% in MeOH, 1.20 mmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E14** was obtained as a mixture of isomers as an orange solid (185 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.40 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-dichloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-143)



(±)-143
$C_{26}H_{22}Cl_2O_6$
MW: 501.36

A mixture of $(CH_3)_4N(OAc)_3BH$ (626 mg, 2.38 mmol, 6.42 eq.) and freshly distilled AcOH (221 µL, 3.86 mmol, 10.4 eq.) in MeCN (9.62 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E14** (185 mg, 370 µmol, 1.00 eq.) in MeCN (6.39 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then performed to obtain the racemic *endo*-product **(±)-143** as a colorless foam (119 mg, 237 µmol) in a yield of 48% over 3 steps.

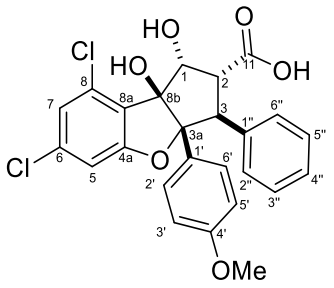
$\mathbf{R}_f$ = 0.21 (petroleum ether/EtOAc 7:3).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.14 (d, J = 1.7 Hz, 1H, *H*-5), 7.07 – 6.95 (m, 8H, *H*-7, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.57 (d, J = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.72 (d, J = 6.1 Hz, 1H, O*H*-1), 5.69 (s, 1H, O*H*-8b), 4.69 (dd, J = 5.8, 4.6 Hz, 1H, *H*-1), 4.38 (d, J = 14.0 Hz, 1H, *H*-3), 4.06 (dd, J = 14.0, 4.5 Hz, 1H, *H*-2), 3.59 (s, 3H, H_3CO-11), 3.58 (s, 3H, H_3CO-4'').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.2 (q, *C*-11), 160.6 (q, *C*-4a), 157.6 (q, *C*-4'), 138.0 (q, *C*-1''), 134.3 (q, *C*-6), 132.5 (q, *C*-8a), 128.5 (t, *C*-2', *C*-6'), 128.0 (q, *C*-1'), 127.9 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 125.8 (t, *C*-4''), 125.6 (q, *C*-8), 120.9 (t, *C*-7), 111.9 (t, *C*-3', *C*-5'), 109.2 (t, *C*-5), 102.3 (q, *C*-3a), 93.5 (q, *C*-8b), 78.2 (t, *C*-1), 54.9 (t, *C*-3), 54.7 (p, H_3CO-4'), 51.7 (t, *C*-2), 51.5 (p, H_3CO-11).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{22}Cl_2O_6Na$ $[M+Na]^+$, 523.0691 found 523.0676.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-Dichloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (E15)



E15

$C_{25}H_{20}Cl_2O_6$

MW: 487.33

A solution of methyl ester **(±)-143** (40.0 mg, 79.8 µmol, 1.00 eq.) and lithium hydroxide solution (2.00 M in H_2O, 203 µL, 407 µmol, 5.10 eq.) in MeOH (1.25 mL) was heated at 50 °C for 2 h. As only a low conversion could be detected by TLC, more lithium hydroxide solution (2.00 M in H_2O, 203 µL, 407 µmol, 5.10 eq.) was added and the mixture was stirred for additional 18 h at 50 °C. The solution was then cooled, acidified with HCl (1.00 M in H_2O) to pH 1-2 and diluted with CH_2Cl_2 (5.00 mL) and H_2O (5.00 mL). The organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2x 5.00 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the rocagloic acid **E15** as a yellowish solid (33.0 mg, 67.7 µmol) in 85% yield.

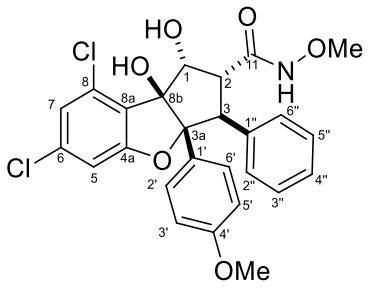
$\mathbf{R}_f$ = 0.52 (EtOAc).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.12 (d, J = 1.7 Hz, 1H, *H*-5), 7.07 – 6.89 (m, 8H, *H*-7, *H*-2', H-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.56 (d, J = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.59 (s, 1H, O*H*-8b), 4.63 (d, J = 4.2 Hz, 1H, *H*-1), 4.34 (d, J = 13.9 Hz, 1H, *H*-3), 3.85 (dd, J = 13.8, 3.9 Hz, 1H, *H*-2), 3.57 (s, 3H, H_3CO-4').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 172.5 (q, *C*-11), 160.8 (q, *C*-4a), 157.6 (q, *C*-4'), 138.5 (q, *C*-1''), 134.2 (q, *C*-6), 132.5 (q, *C*-8a), 128.5 (t, *C*-2', *C*-6'), 128.4 (q, *C*-1'), 128.1 (t, *C*-3'', *C*-5''), 127.4 (t, *C*-2'', *C*-6''), 126.0 (q, *C*-8), 125.7 (t, *C*-4''), 120.8 (t, *C*-7), 111.9 (t, *C*-3', *C*-5'), 109.1 (t, *C*-5), 102.7 (q, *C*-3a), 93.7 (q, *C*-8b), 78.1 (t, *C*-1), 55.7 (t, *C*-3), 54.8 (p, H_3CO-4'), 51.9 (t, *C*-2).

HRMS (ESI$^-$) *m/z* calcd. for $C_{25}H_{19}Cl_2O_6$ $[M-H]^-$ 485.0559, found 485.0575.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-Dichloro-1,8b-dihydroxy-*N*-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-145)



(±)-145
$C_{26}H_{23}Cl_2NO_6$
MW: 516.37

To a solution of rocagloic acid **E15** (17.6 mg, 36.1 µmol, 1.00 eq.) in CH_2Cl_2 (2.58 mL) EDC·HCl (10.4 mg, 54.2 µmol, 1.50 eq.), HOBt·H_2O (7.7 mg, 48.4 µmol, 1.35 eq.), methoxylamine hydrochloride (15.1 mg, 181 µmol, 5.00 eq.) and triethylamine (25.0 µL, 181 µmol, 5.00 eq.) were added. The mixture was stirred at rt for 12 h. Subsequently, the reaction was terminated by the addition of HCl (1.00 M in H_2O), extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 ⟶ 95:5). The desired rocagloic amide **(±)-145** was obtained as a colorless solid (5.7 mg, 11.0 µmol) in 31% yield.

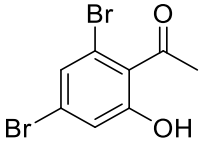
$\mathbf{R}_f$ = 0.48 (CH_2Cl_2/MeOH 95:5).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 11.27 (s, 1H, N*H*OCH$_3$), 7.14 (d, $\mathcal{J}$ = 1.5 Hz, 1H, *H*-5), 7.07 – 6.95 (m, 8H, *H*-7, *H*-2', H-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.59 (d, $\mathcal{J}$ = 9.1 Hz, 2H, *H*-3', *H*-5'), 5.60 (s, 1H, O*H*-8b), 5.34 (d, $\mathcal{J}$ = 5.4 Hz, 1H, O*H*-1), 4.55 (t, $\mathcal{J}$ = 4.7 Hz, 1H, *H*-1), 4.40 (d, $\mathcal{J}$ = 14.1 Hz, 1H, *H*-3), 3.67 (dd, $\mathcal{J}$ = 14.1, 4.2 Hz, 1H, *H*-2), 3.59 (s, 3H, *H*$_3$CO-4'), 3.52 (s, 3H, NHOC*H*$_3$).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 166.3 (q, *C*-11), 160.7 (q, *C*-4a), 157.7 (q, *C*-4'), 137.9 (q, *C*-1''), 134.2 (q, *C*-6), 132.6 (q, *C*-8a), 128.4 (t, *C*-2', *C*-6'), 128.1 (q, *C*-1'), 127.9 (t, *C*-3'', *C*-5''), 127.4 (t, *C*-2'', *C*-6''), 126.9 (t, *C*-4''), 125.8 (q, *C*-8), 120.8 (t, *C*-7), 111.9 (t, *C*-3', *C*-5'), 109.1 (t, *C*-5), 102.0 (q, *C*-3a), 93.8 (q, *C*-8b), 78.4 (t, *C*-1), 63.2 (p, NHO*C*H$_3$), 54.9 (t, *C*-3), 54.8 (p, H$_3$*C*O-4'), 48.9 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{23}Cl_2NO_6Na$ $[M+Na]^+$ 538.0800, found 538.0794.

1-(2,4-Dibromo-6-hydroxyphenyl)ethan-1-one (138)



138
$C_8H_6Br_2O_2$
MW: 293.94

To a solution of the 3,5-dibromophenol (**136**) (3.00 g, 11.9 mmol, 1.00 eq.) and dry pyridine (1.44 mL, 17.9 mmol, 1.50 eq.) in dry CH_2Cl_2 (15.9 mL) was slowly added acetyl chloride (1.10 mL, 15.5 mmol, 1.30 eq.) and the reaction was stirred at rt for 30 min. Then, $NaHCO_3$ solution (aq., sat.) was added and

the mixture was extracted with CH_2Cl_2 (3x), washed with H_2O, dried over $MgSO_4$, filtered and concentrated to yield 3,5-dibromophenyl acetate which was used without further purification. To the compound was added $AlCl_3$ (2.06 g, 15.5 mmol, 1.30 eq.) and the mixture was heated to 150 °C with stirring for 10 min. The reaction mixture was allowed to cool to rt and dissolved in EtOAc before careful terminating with H_2O. After phase separation, the aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish the crude product as an oil that crystallized on standing. After recrystallization from EtOH, acetophenone **138** was obtained as a light brown solid (2.26 g, 7.67 mmol) in 64% yield.

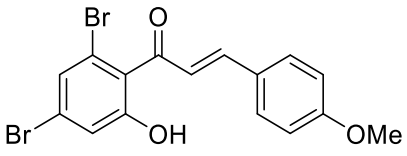
$\mathbf{R}_f$ = 0.41 (petroleum ether/EtOAc 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 12.23 (s, 1H, O*H*), 7.37 (d, J = 1.9 Hz, 1H, Ar*H*), 7.15 (d, J = 1.9 Hz, 1H, Ar*H*), 2.86 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 205.2 (q, *C*=O), 163.6 (q, Ar*C*), 129.0 (q, Ar*C*), 128.7 (t, Ar*C*H), 123.7 (q, Ar*C*), 121.4 (t, Ar*C*H), 118.0 (q, Ar*C*), 33.4 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[232]

(*E*)-1-(2,4-Dibromo-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (140)



140

$C_{16}H_{12}Br_2O_3$

MW: 412.08

Acetophenone **138** (717 mg, 2.44 mmol, 1.00 eq.) was added to a solution of NaOEt (498 mg, 7.32 mmol, 3.00 eq.) in EtOH (8.41 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (296 µL, 2.44 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **140** was obtained as a yellow solid (923 mg, 2.24 mmol) in 92% yield.

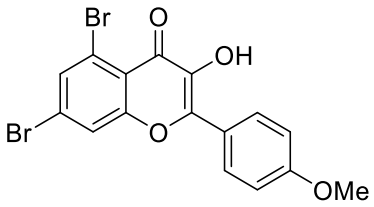
$\mathbf{R}_f$ = 0.36 (petroleum ether/EtOAc 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 10.94 (s, 1H, O*H*), 7.78 (d, J = 15.5 Hz, 1H, C(O)CH=C*H*), 7.60 (d, J = 8.7 Hz, 2H, 2x Ar*H*), 7.46 (d, J = 15.5 Hz, 1H, C(O)C*H*), 7.38 (d, J = 1.7 Hz, 1H, Ar*H*), 7.17 (d, J = 1.8 Hz, 1H, Ar*H*), 6.95 (d, J = 8.7 Hz, 2H, 2x Ar*H*), 3.87 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 194.2 (q, *C*=O), 162.4 (q, Ar*C*), 161.8 (q, Ar*C*), 144.6 (t, C(O)CH=*C*H), 131.0 (t, 2x Ar*C*H), 128.3 (t, Ar*C*H), 127.8 (q, Ar*C*), 127.4 (q, Ar*C*), 123.5 (t, C(O)*C*H), 122.9 (q, Ar*C*), 122.5 (q, Ar*C*), 120.7 (t, Ar*C*H), 114.8 (t, 2x Ar*C*H), 55.6 (p, O*C*H$_3$).

HRMS (ESI$^-$) *m/z* calcd. for $C_{16}H_{11}O_3Br$ $[M-H]^-$ 408.9075, found 408.9068.

5,7-Dibromo-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (142)



142
$C_{16}H_{10}Br_2O_4$
MW: 426.06

To a suspension of chalcone **140** (824 mg, 2.00 mmol, 1.00 eq.) in MeOH (17.2 mL), NaOH (3.00 M, aq., 2.58 mL, 7.74 mmol, 3.87 eq.) was added and cooled to 0 °C. H_2O_2 (30 wt% in H_2O, 652 µL, 6.40 mmol, 3.20 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 20 h. Then, HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate. Subsequently, the suspension was extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOAc to give the desired product **142** as a pale-yellowish solid (125 mg, 293 µmol) in 15% yield.

$\mathbf{R}_f$ = 0.39 (petroleum ether/EtOAc 4:1).

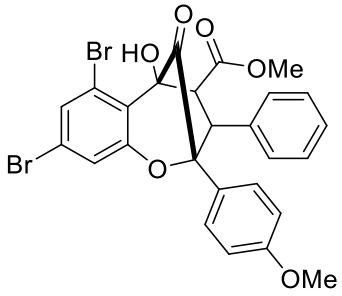
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.18 (d, J = 9.0 Hz, 2H, 2x Ar*H*), 7.78 (d, J = 1.8 Hz, 1H, Ar*H*), 7.75 (d, J = 1.8 Hz, 1H, Ar*H*), 7.04 (d, J = 9.0 Hz, 2H, 2x Ar*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 171.7 (q, *C*=O), 161.5 (q, Ar*C*), 156.3 (q, Ar*C*), 144.1 (q, *C*=COH), 138.0 (q, *C*OH), 133.7 (t, Ar*C*H), 129.5 (t, 2x Ar*C*H), 126.9 (q, Ar*C*), 122.7 (q, Ar*C*), 121.3 (t, Ar*C*H), 121.2 (q, Ar*C*), 117.6 (q, Ar*C*), 114.4 (q, 2x Ar*C*H), 55.6 (p, O*C*H$_3$).

HRMS (EI) *m/z* calcd. for $C_{16}H_{10}Cl_2O_4$ $[M]^+$ 423.8946, found 423.8943.

The analytical data are consistent with those reported in the literature.[105]

(±)-Methyl (3*S*,4*S*,5*R*)-6,8-dibromo-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]oxepine-4-carboxylate (E16)



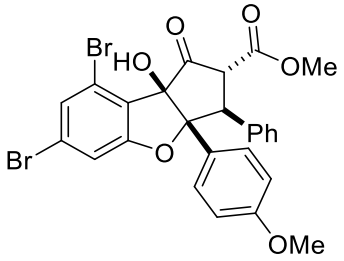
E16
$C_{26}H_{20}Br_2O_6$
MW: 588.25

Methyl cinnamate (665 mg, 4.10 mmol, 14.2 eq.) was added to a solution of flavonol **142** (123 mg, 289 µmol, 1.00 eq.) in dry chloroform (5.66 mL) and freshly distilled 2,2,2-trifluoroethanol (2.41 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed

under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 9:1 ⟶ 1:1). Product **E16** was obtained as a mixture of isomers as a yellowish solid (170 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.24 – 0.72 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-6,8-dibromo-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E17)

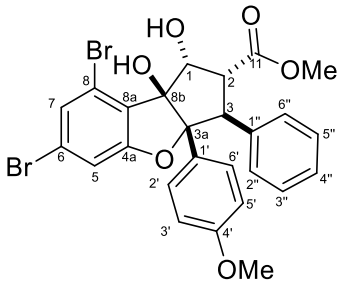


E17
$C_{26}H_{20}Br_2O_6$
MW: 588.25

Cycloadduct **E16** (170 mg, 289 µmol, 1.00 eq.) was dissolved in MeOH (10.7 mL). Then, NaOMe solution (156 µL, 25 wt% in MeOH, 939 µmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E17** was obtained as a mixture of isomers as an orange solid (158 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.48 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-dibromo-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-144)



(±)-144
$C_{26}H_{22}Br_2O_6$
MW: 590.26

A mixture of $(CH_3)_4N(OAc)_3BH$ (454 mg, 1.72 mmol, 6.42 eq.) and freshly distilled AcOH (160 µL, 2.80 mmol, 10.4 eq.) in MeCN (6.98 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E17** (158 mg, 269 µmol, 1.00 eq.) in MeCN (4.63 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and

concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then performed to obtain the racemic *endo*-product **(±)-143** as a pale-yellow foam (84.8 mg, 144 µmol) in 50% yield over 3 steps.

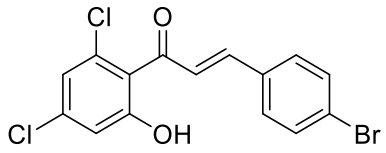
$\mathbf{R}_f$ = 0.26 (petroleum ether/EtOAc 7:3).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.30 (d, $\mathcal{J}$ = 1.5 Hz, 1H, *H*-5), 7.26 (d, $\mathcal{J}$ = 1.5 Hz, 1H, *H*-7), 7.07 – 7.03 (m, 2H, *H*-2'', *H*-6''), 6.99 – 6.96 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.56 (dt, $\mathcal{J}$ = 9.9, 2.5 Hz, 2H, *H*-3', *H*-5'), 5.65 (t, $\mathcal{J}$ = 3.0 Hz, 2H, *H*O-1, *H*O-8b), 4.68 (dd, $\mathcal{J}$ = 5.9, 4.4 Hz, 1H, *H*-1), 4.41 (d, $\mathcal{J}$ = 13.9 Hz, 1H, *H*-3), 4.05 (dd, $\mathcal{J}$ = 14.0, 4.3 Hz, 1H, *H*-2), 3.59 (s, 3H, H_3CO-11), 3.56 (s, 3H, H_3CO-4').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.3 (q, *C*-11), 160.9 (q, *C*-4a), 157.6 (q, *C*-4'), 138.0 (q, *C*-1''), 128.5 (t, *C*-2', *C*-6'), 128.1 (q, C-1'), 127.9 (t, *C*-3'', *C*-5''), 127.7 (q, *C*-8a), 127.5 (t, *C*-2'', *C*-6''), 126.3 (t, *C*-7), 125.8 (t, *C*-4''), 122.3 (q, *C*-6), 121.1 (q, *C*-8), 112.3 (t, *C*-5), 111.8 (t, *C*-3', *C*-5'), 102.3 (q, *C*-3a), 94.0 (q, *C*-8b), 77.9 (t, *C*-1), 54.9 (t, *C*-3), 54.7 (p, H_3CO-4'), 51.57 (t, *C*-2), 51.5 (p, H_3CO-11).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{22}Br_2O_6Na$ $[M+Na]^+$ 610.9681 found 610.9686.

(*E*)-3-(4-Bromophenyl)-1-(2,4-dichloro-6-hydroxyphenyl)prop-2-en-1-one (146)



146

$C_{15}H_9BrCl_2O_2$

MW: 372.04

Acetophenone **137** (500 mg, 2.44 mmol, 1.00 eq.) was added to a solution of NaOEt (498 mg, 7.32 mmol, 3.00 eq.) in EtOH (8.41 mL). After stirring for 1 h at rt, 4-bromobenzaldehyde (451 mg, 2.44 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **146** was obtained as a yellow solid (856 mg, 2.30 mmol) in 94% yield.

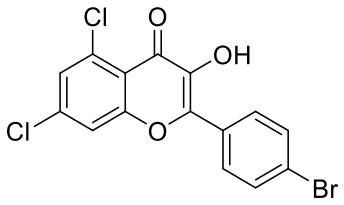
$\mathbf{R}_f$ = 0.57 (petroleum ether/EtOAc 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 11.51 (s, 1H, O*H*), 7.73 (d, $\mathcal{J}$ = 15.6 Hz, 1H, C(O)CH=C*H*), 7.61 (d, $\mathcal{J}$ = 15.6 Hz, 1H, C(O)C*H*), 7.57 (d, $\mathcal{J}$ = 8.4 Hz, 2H, 2x Ar*H*), 7.48 (d, $\mathcal{J}$ = 8.4 Hz, 2H, 2x Ar*H*), 7.02 (d, $\mathcal{J}$ = 2.0 Hz, 1H, Ar*H*), 6.98 (d, $\mathcal{J}$ = 2.0 Hz, 1H, Ar*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.7 (q, *C*=O), 163.0 (q, Ar*C*), 143.1 (t, C(O)CH=*C*H), 140.3 (q, Ar*C*), 134.8 (q, Ar*C*), 133.5 (q, Ar*C*), 132.51 (t, 2x Ar*C*H), 130.2 (t, 2x Ar*C*H), 126.5 (t, C(O)*C*H), 125.6 (q, ArC), 122.5 (t, ArC*H*), 119.9 (q, Ar*C*), 117.5 (t, Ar*C*H).

HRMS (ESI$^-$) *m/z* calcd. for $C_{15}H_8BrCl_2O_2$ $[M-H]^-$ 368.9085, found 368.9085.

2-(4-Bromophenyl)-5,7-dichloro-3-hydroxy-4*H*-chromen-4-one (147)



147
$C_{15}H_7BrCl_2O_3$
MW: 386.02

To a suspension of chalcone **146** (744 mg, 2.00 mmol, 1.00 eq.) in MeOH (17.2 mL), NaOH (3.00 M, aq., 2.58 mL, 7.74 mmol, 3.87 eq.) was added and cooled to 0 °C. H_2O_2 (30 wt% in H_2O, 652 µL, 6.40 mmol, 3.20 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 20 h. Then, HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate. Subsequently, the suspension was extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOAc to give the desired product **147** as a pale-yellowish solid (155 mg, 402 µmol) in 20% yield.

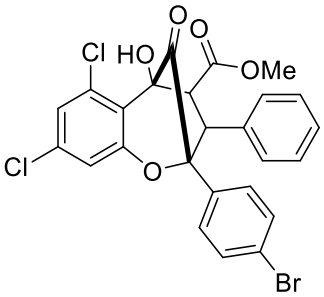
$\mathbf{R}_f$ = 0.57 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.09 (d, J = 8.4 Hz, 2H, 2x Ar*H*), 7.67 (d, J = 8.2 Hz, 2H, 2x Ar*H*), 7.56 (s, 1H, Ar*H*), 7.43 (s, 1H, Ar*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 171.9 (q, *C*=O), 156.7 (q, Ar*C*), 142.7 (q, *C*=COH), 139.2 (q, Ar*C*), 139.0 (q, *C*OH), 134.7 (q, Ar*C*), 132.2 (t, 2x Ar*C*H), 129.3 (q, Ar*C*), 129.1 (t, 2x Ar*C*H), 127.8 (t, Ar*C*H), 125.3 (q, Ar*C*), 117.6 (t, Ar*C*H), 116.5 (q, Ar*C*).

HRMS (EI) *m/z* calcd. for $C_{15}H_7BrCl_2O_3$ $[M]^+$ 335.9956, found 335.8955.

(±)-Methyl (3*S*,4*S*,5*R*)-2-(4-bromophenyl)-6,8-dichloro-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E18)



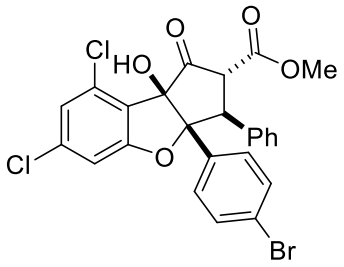
E18
$C_{25}H_{17}BrCl_2O_5$
MW: 548.21

Methyl cinnamate (1.29 g, 7.98 mmol, 14.2 eq.) was added to a solution of flavonol **147** (217 mg, 562 µmol, 1.00 eq.) in dry chloroform (11.0 mL) and freshly distilled 2,2,2-trifluoroethanol (4.68 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column

chromatography (petroleum ether/EtOAc 1:0 ⟶ 3:1). Product **E18** was obtained as a mixture of isomers as a yellowish oil (235 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.31 – 0.80 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-3a-(4-bromophenyl)-6,8-dichloro-8b-hydroxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E19)

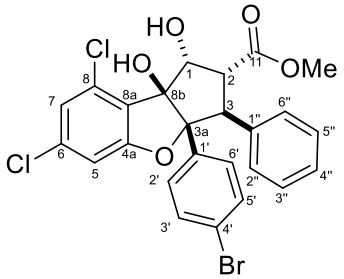


E19
$C_{25}H_{17}BrCl_2O_5$
MW: 548.21

Cycloadduct **E18** (235 mg, 429 µmol, 1.00 eq.) was dissolved in MeOH (15.9 mL). Then, NaOMe solution (232 µL, 25 wt% in MeOH, 1.39 mmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E19** was obtained as a mixture of isomers as a yellowish solid (155 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.56 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6,8-dichloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-148)



(±)-148
$C_{25}H_{19}BrCl_2O_5$
MW: 550.23

A mixture of $(CH_3)_4N(OAc)_3BH$ (478 mg, 1.82 mmol, 6.42 eq.) and freshly distilled AcOH (168 µL, 2.94 mmol, 10.4 eq.) in MeCN (7.34 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E19** (155 mg, 283 µmol, 1.00 eq.) in MeCN (4.87 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then

performed to obtain the racemic *endo*-product **(±)-148** as a colorless foam (12.0 mg, 21.8 µmol) in 4% yield over 3 steps.

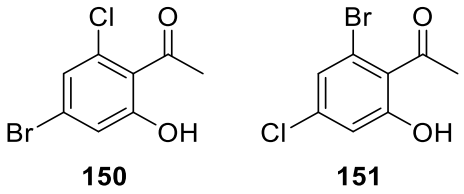
$\mathbf{R}_f$ = 0.38 (petroleum ether/EtOAc 7:3).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.20 (d, J = 8.7 Hz, 2H, *H*-3', *H*-5'), 7.17 (d, J = 1.6 Hz, 1H, *H*-5), 7.09 – 6.97 (m, 8H, *H*-7, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 5.85 (s, 1H, *H*O-8b), 5.77 (d, J = 6.1 Hz, 1H, *H*O-1), 4.68 (t, J = 5.0 Hz, 1H, *H*-1), 4.43 (d, J = 13.9 Hz, 1H, *H*-3), 4.11 (dd, J = 13.9, 4.4 Hz, 1H, *H*-2), 3.59 (s, 3H, C*H*$_3$O-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.1 (q, *C*-11), 160.4 (q, *C*-4a), 137.6 (q, *C*-1''), 135.6 (q, *C*-1'), 134.4 (q, *C*-6), 132.3 (q, *C*-8a), 129.6 (t, *C*-2', *C*-6'), 129.3 (t, *C*-3', *C*-5'), 127.8 (t, *C*-3'', *C*-5''), 127.6 (t, *C*-2'', *C*-6''), 126.0 (t, *C*-4''), 125.3 (q, *C*-8), 121.1 (t, *C*-7), 119.9 (q, *C*-4'), 109.3 (t, *C*-5), 102.1 (q, *C*-3a), 93.7 (q, *C*-8b), 78.1 (t, *C*-1), 54.9 (t, *C*-3), 51.7 (t, *C*-2), 51.6 (p, H$_3$*C*O-11).

HRMS (ESI$^+$) *m/z* calcd. for $C_{25}H_{19}BrCl_2O_5Na$ $[M+Na]^+$ 570.9702 found 570.9691.

1-(4-Bromo-2-chloro-6-hydroxyphenyl)ethan-1-one (150) and 1-(2-Bromo-4-chloro-6-hydroxyphenyl)ethan-1-one (151)



150 **151**

$C_8H_6BrClO_2$
MW: 249.49

To a solution of the 3-bromo-5-chlorophenol (**149**) (4.00 g, 19.3 mmol, 1.00 eq.) and dry pyridine (1.44 mL, 2.33 mmol, 1.50 eq.) in dry CH_2Cl_2 (25.7 mL) was slowly added acetyl chloride (1.79 mL, 25.1 mmol, 1.30 eq.) and the reaction was stirred at rt for 30 min. Then, $NaHCO_3$ solution (aq., sat.) was added and the mixture was extracted with CH_2Cl_2 (3x), washed with H_2O, dried over $MgSO_4$, filtered and concentrated to yield 3-bromo-5-chlorophenyl acetate which was used without further purification. To the compound was added $AlCl_3$ (3.34 g, 25.1 mmol, 1.30 eq.) and the mixture was heated to 150 °C with stirring for 10 min. The reaction mixture was allowed to cool to rt and dissolved in EtOAc before careful terminating with H_2O. After phase separation, the aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish the crude product as an oil that crystallized on standing. After recrystallization from EtOH, the mixture of isomers was separated by column chromatography (petroleum ether/EtOAc 19:1) to yield 1-(4-Bromo-2-chloro-6-hydroxyphenyl)ethan-1-one (**150**) as a pale-yellow oily solid (2.07 g, 8.30 mmol, 43%) and 1-(2-Bromo-4-chloro-6-hydroxyphenyl)ethan-1-one (**151**) as a pale-yellow solid (1.07 g, 4.29 mmol, 22%).

1-(4-Bromo-2-chloro-6-hydroxyphenyl)ethan-1-one (150)

$\mathbf{R}_f$ = 0.53 (petroleum ether/EtOAc 10:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 12.69 (s, 1H, O*H*), 7.15 (d, J = 2.0 Hz, 1H, Ar*H*), 7.12 (d, J = 1.9 Hz, 1H, Ar*H*), 2.83 (s, 3H, C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.8 (q, *C*=O), 164.3 (q, Ar*C*), 153.8 (q, Ar*C*), 136.0 (q, Ar*C*), 129.0 (q, Ar*C*), 125.3 (t, Ar*C*H), 121.0 (t, Ar*C*H), 33.8 (p, *C*H_3).

HRMS (ESI$^-$) *m/z* calcd. for $C_6H_5BrOClO_2$ $[M-H]^-$ 246.9161 found 246.9158.

1-(2-Bromo-4-chloro-6-hydroxyphenyl)ethan-1-one (151)

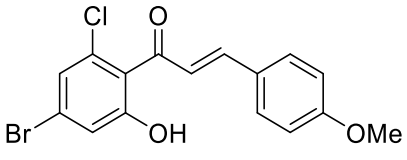
R$_f$ = 0.29 (petroleum ether/EtOAc 10:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 12.23 (s, 1H, O*H*), 7.37 (d, J = 1.9 Hz, 1H, Ar*H*), 7.15 (d, J = 1.9 Hz, 1H, Ar*H*), 2.86 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 205.0 (q, *C*=O), 163.9 (q, Ar*C*), 140.7 (q, Ar*C*), 126.1 (t, Ar*C*H), 123.8 (q, Ar*C*), 120.6 (q, Ar*C*), 118.3 (t, Ar*C*H), 33.4 (p, *C*H_3).

HRMS (ESI$^-$) *m/z* calcd. for $C_6H_5BrOClO_2$ $[M-H]^-$ 246.9161 found 246.9165.

(*E*)-1-(4-Bromo-2-chloro-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (152)



152
$C_{16}H_{12}BrClO_3$
MW: 367.62

Acetophenone **150** (1.19 g, 4.77 mmol, 1.00 eq.) was added to a solution of NaOEt (970 mg, 14.3 mmol, 3.00 eq.) in EtOH (16.0 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (580 µL, 4.77 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **152** was obtained as a yellow solid (1.62 g, 4.59 mmol) in 96% yield.

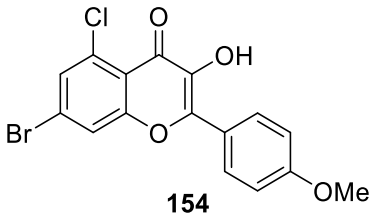
R$_f$ = 0.33 (petroleum ether/EtOAc 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 11.49 (bs, 1H, O*H*), 7.81 (d, J = 15.5 Hz, 1H, C(O)CH=C*H*), 7.59 (d, J = 8.8 Hz, 2H, 2x Ar*H*), 7.49 (d, J = 15.5 Hz, 1H, C(O)C*H*), 7.16 (d, J = 1.8 Hz, 1H, Ar*H*), 7.13 (d, J = 1.8 Hz, 1H, Ar*H*), 6.94 (d, J = 8.8 Hz, 2H, 2x Ar*H*), 3.86 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.7 (q, *C*=O), 162.6 (q, Ar*C*), 162.4 (q, Ar*C*), 144.9 (t, C(O)CH=*C*H), 134.6 (q, Ar*C*), 131.0 (t, 2x Ar*C*H), 127.8 (q, Ar*C*), 127.4 (q, Ar*C*), 125.0 (t, Ar*C*H), 123.6 (t, C(O)*C*H), 120.7 (q, Ar*C*), 120.3 (t, Ar*C*H), 114.7 (t, 2x Ar*C*H), 55.6 (p, O*C*H_3).

HRMS (ESI$^-$) *m/z* calcd. for $C_{16}H_{11}O_3ClBr$ $[M-H]^-$ 364.9580, found 364.9582.

7-Bromo-5-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (154)



154

$C_{16}H_{10}BrClO_4$

MW: 381.61

To a suspension of chalcone **152** (1.62 g, 4.42 mmol, 1.00 eq.) in MeOH (53.3 mL), NaOH (3.00 M, aq., 7.58 mL, 22.7 mmol, 5.15 eq.) was added and cooled to 0 °C. H_2O_2 (35 wt% in H_2O., 1.46 mL, 17.0 mmol, 3.84 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 18 h. Then, HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate. Subsequently, the suspension was extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOH to give the desired product **154** as a yellow solid (203 mg, 531 µmol) in 12% yield.

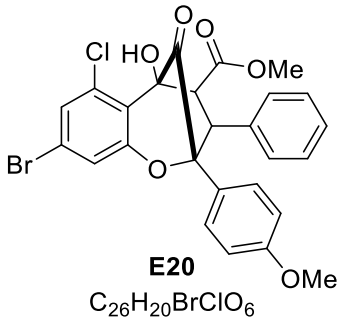
$\mathbf{R}_f$ = 0.30 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 8.18 (dt, J = 9.9, 2.6 Hz, 2H, 2x Ar*H*), 7.71 (d, J = 1.8 Hz, 1H, Ar*H*), 7.54 (d, J = 1.8 Hz, 1H, Ar*H*), 7.17 (bs, 1H, *OH*), 7.04 (dt, J = 9.9, 2.6 Hz, 2H, 2x Ar*H*), 3.90 (3H, OC*H*$_3$).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 171.7 (q, *C*=O), 161.5 (q, Ar*C*), 156.5 (q, Ar*C*), 144.1 (q, *C*=COH), 138.2 (q, *C*OH), 134.4 (q, Ar*C*), 130.2 (t, Ar*C*H), 129.6 (t, 2x Ar*C*H), 126.4 (q, Ar*C*), 122.7 (q, Ar*C*), 120.6 (t, Ar*C*H), 116.9 (q, Ar*C*), 114.4 (t, 2x Ar*C*H), 55.6 (p, O*C*H$_3$).

HRMS (EI) *m/z* calcd. for $C_{16}H_{10}ClO_4Br$ $[M]^+$ 379.9451, found 379.9469.

(±)-Methyl (3*S*,4*S*,5*R*)-8-bromo-6-chloro-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E20)



E20

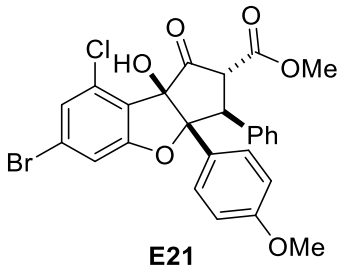
$C_{26}H_{20}BrClO_6$

MW: 543.79

Methyl cinnamate (1.17 g, 7.20 mmol, 14.2 eq.) was added to a solution of flavonol **154** (194 mg, 507 µmol, 1.00 eq.) in dry chloroform (10.4 mL) and freshly distilled 2,2,2-trifluoroethanol (4.14 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (14 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 5:1 → 1:1). Product **E20** was obtained as a mixture of isomers as a yellowish solid (262 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.29 – 0.51 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-6-bromo-8-chloro-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E21)

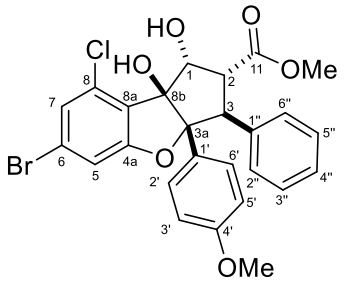


E21
$C_{26}H_{20}BrClO_6$
MW: 543.79

Cycloadduct **E20** (262 mg, 482 µmol, 1.00 eq.) was dissolved in MeOH (19.3 mL). Then, NaOMe solution (377 µL, 25 wt% in MeOH, 1.59 mmol, 3.30 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E21** was obtained as a mixture of isomers as an orange solid (262 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.66 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-bromo-8-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-156)



(±)-156
$C_{26}H_{22}BrClO_6$
MW: 545.81

A mixture of $(CH_3)_4N(OAc)_3BH$ (814 mg, 3.09 mmol, 6.42 eq.) and freshly distilled AcOH (288 µL, 5.02 mmol, 10.4 eq.) in MeCN (4.25 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E21** (262 mg, 482 µmol, 1.00 eq.) in MeCN (2.83 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then

performed to obtain the racemic *endo*-product **(±)-156** as a colorless foam (153 mg, 280 µmol) in 55% yield over 3 steps.

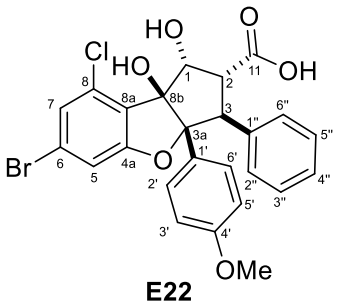
$\mathbf{R}_f$ = 0.32 (petroleum ether/EtOAc 7:3).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.27 (d, $\mathcal{J}$ = 1.5 Hz, 1H, *H*-5), 7.14 (d, $\mathcal{J}$ = 1.5 Hz, 1H, *H*-7), 7.07 – 6.95 (m, 7H, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.57 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.72 (d, $\mathcal{J}$ = 6.2 Hz, 1H, *H*O-1), 5.69 (s, 1H, *H*O-8b), 4.69 (dd, $\mathcal{J}$ = 6.0, 4.6 Hz, 1H, *H*-1), 4.37 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 4.05 (dd, $\mathcal{J}$ = 14.1, 4.4 Hz, 1H, *H*-2), 3.59 (s, 3H, H_3CO-11), 3.58 (s, 3H, H_3CO-4').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.2 (q, *C*-11), 160.8 (q, *C*-4a), 157.6 (q, *C*-4'), 138.0 (q, *C*-1''), 132.8 (q, *C*-8a), 128.5 (t, *C*-2', *C*-6'), 128.0 (q, C-1'), 127.9 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 126.1 (t, *C*-8), 125.8 (t, *C*-4''), 123.5 (q, *C*-7), 122.2 (q, *C*-6), 112.0 (t, *C*-5), 111.9 (t, *C*-3', *C*-5'), 102.2 (q, *C*-3a), 93.6 (q, *C*-8b), 78.1 (t, *C*-1), 54.9 (t, *C*-3), 54.7 (p, H$_3$*C*O-4'), 51.7 (t, *C*-2), 51.5 (p, H$_3$*C*O-11).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{22}BrClO_6Na$ $[M+Na]^+$ 567.0186 found 567.0181.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-Bromo-8-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (E22)



E22

$C_{25}H_{20}BrClO_6$

MW: 531.78

A solution of methyl ester **(±)-156** (68.2 mg, 125 µmol, 1.00 eq.) and lithium hydroxide solution (2.00 M in H_2O, 319 µL, 637 µmol, 5.10 eq.) in MeOH (10.1 mL) was heated at 50 °C for 28 h. Then, the solution was cooled, acidified with HCl (1.00 M in H_2O) to pH 1-2 and diluted with CH_2Cl_2 (10.0 mL) and H_2O (10.0 mL). The organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2x 5.00 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the rocagloic acid **E22** as a yellowish solid (59.6 mg, 112 µmol) in 90% yield.

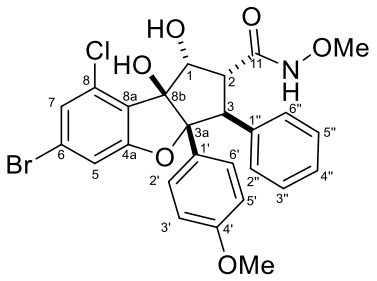
$\mathbf{R}_f$ = 0.56 (EtOAc).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 12.20 (bs, 1H, CO_2H), 7.25 (d, $\mathcal{J}$ = 1.6 Hz, 1H, *H*-5), 7.12 (d, $\mathcal{J}$ = 1.6 Hz, 1H, *H*-7), 7.07 – 6.94 (m, 7H, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.56 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.60 (s, 1H, *H*O-8b), 4.65 (d, $\mathcal{J}$ = 4.3 Hz, 1H, *H*-1), 4.34 (d, $\mathcal{J}$ = 13.9 Hz, 1H, *H*-3), 3.89 (dd, $\mathcal{J}$ = 13.9, 4.3 Hz, 1H, *H*-2), 3.58 (s, 3H, H_3CO-4').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 171.8 (q, *C*-11), 160.9 (q, *C*-4a), 157.6 (q, *C*-4'), 138.5 (q, *C*-1''), 132.7 (q, *C*-8a), 128.5 (t, *C*-2', *C*-6'), 128.3 (q, C-1'), 128.0 (t, *C*-3'', *C*-5''), 127.4 (t, *C*-2'', *C*-6''), 126.3 (q, *C*-8), 125.7 (t, *C*-4''), 123.4 (t, *C*-7), 122.0 (q, *C*-6), 111.8 (t, *C*-5, *C*-3', *C*-5'), 102.5 (q, *C*-3a), 93.7 (q, *C*-8b), 78.1 (t, *C*-1), 55.3 (t, *C*-3), 54.7 (p, H$_3$*C*O-4'), 51.8 (t, *C*-2).

HRMS (ESI$^-$) *m/z* calcd. for $C_{25}H_{19}ClBrO_6$ $[M-H]^-$ 529.0054, found 529.0057.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-Bromo-8-chloro-1,8b-dihydroxy-*N*-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-158)



(±)-158
$C_{26}H_{23}BrClNO_6$
MW: 560.83

To a solution of rocagloic acid **E22** (70.0 mg, 132 µmol, 1.00 eq.) in CH_2Cl_2 (9.08 mL) EDC·HCl (37.9 mg, 197 µmol, 1.50 eq.), HOBt·H_2O (31.6 mg, 178 µmol, 1.35 eq.) and triethylamine (91.7 µL, 658 µmol, 5.00 eq.) were added and was stirred at rt. After 1 h, methoxylamine hydrochloride (55.0 mg, 658 µmol, 5.00 eq.) was added and reaction mixture was stirred for additional 18 h. The reaction was terminated by addition of HCl (1.00 M in H_2O), extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 98:2). The desired rocagloic amide **(±)-158** was obtained as a colorless solid (58.0 mg, 103 µmol) in 79% yield.

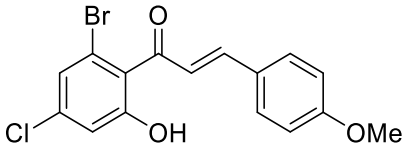
$\mathbf{R}_f$ = 0.32 (CH_2Cl_2/MeOH 95:5).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 11.28 (s, 1H, NHOCH$_3$), 7.26 (d, J = 1.6 Hz, 1H, *H*-5), 7.13 (d, J = 1.6 Hz, 1H, *H*-7), 7.07 – 6.95 (m, 7H, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.59 (d, J = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.60 (s, 1H, *H*O-8b), 5.34 (d, J = 5.4 Hz, 1H, *H*O-1), 4.55 (d, J = 4.8 Hz, 1H, *H*-1), 4.30 (d, J = 14.1 Hz, 1H, *H*-3), 3.68 (dd, J = 14.1, 4.2 Hz, 1H, *H*-2), 3.59 (s, 3H, H_3CO-4'), 3.52 (s, 3H, NHOCH_3).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 166.3 (q, *C*-11), 160.8 (q, *C*-4a), 157.7 (q, *C*-4'), 137.9 (q, *C*-1''), 132.9 (q, *C*-8a), 128.5 (t, *C*-2', *C*-6'), 128.1 (q, C-1'), 127.9 (t, *C*-3'', *C*-5''), 127.4 (t, *C*-2'', *C*-6''), 126.2 (q, *C*-8), 125.9 (t, *C*-4''), 123.5 (q, *C*-7), 122.1 (q, *C*-6), 112.0 (t, *C*-5), 111.9 (t, *C*-3', *C*-5'), 101.9 (q, *C*-3a), 93.9 (q, *C*-8b), 78.4 (t, *C*-1), 63.2 (p, NHO*C*H$_3$), 54.9 (t, *C*-3), 54.8 (p, H$_3$*C*O-4'), 48.9 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{23}NO_6ClBrNa$ $[M+Na]^+$ 582.0295, found 582.0272.

(*E*)-1-(2-Bromo-4-chloro-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (153)



153
$C_{16}H_{12}BrClO_3$
MW: 367.62

Acetophenone **151** (900 mg, 3.61 mmol, 1.00 eq.) was added to a solution of NaOEt (736 mg, 10.8 mmol, 3.00 eq.) in EtOH (68.5 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (439 µL, 3.61 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **153** was obtained as a yellow solid (287 mg, 781 µmol) in 22% yield.

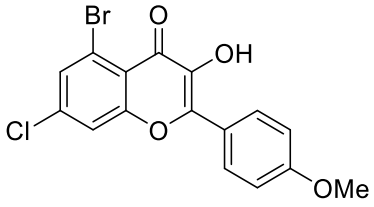
$\mathbf{R}_f$ = 0.62 (petroleum ether/EtOAc 3:2).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 11.04 (bs, 1H, O*H*), 7.78 (d, $\mathcal{J}$ = 15.5 Hz, 1H, C(O)CH=C*H*), 7.60 (d, $\mathcal{J}$ = 8.7 Hz, 2H, 2x Ar*H*), 7.47 (d, $\mathcal{J}$ = 15.5 Hz, 1H, C(O)C*H*), 7.23 (d, $\mathcal{J}$ = 2.0 Hz, 1H, Ar*H*), 7.00 (d, $\mathcal{J}$ = 2.0 Hz, 1H, Ar*H*), 6.95 (d, $\mathcal{J}$ = 8.8 Hz, 2H, 2x Ar*H*), 3.87 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 194.1 (q, *C*=O), 162.4 (q, Ar*C*), 162.0 (q, Ar*C*), 144.5 (t, C(O)CH=*C*H), 139.7 (q, Ar*C*), 131.0 (t, 2x Ar*C*H), 127.5 (q, Ar*C*), 125.6 (t, Ar*C*H), 123.6 (t, C(O)*C*H), 122.54 (q, Ar*C*), 122.53 (q, Ar*C*), 120.7 (t, Ar*C*H), 117.7 (t, Ar*C*H), 114.8 (t, 2x Ar*C*H), 55.6 (p, O*C*H_3).

HRMS (ESI$^+$) *m/z* calcd. for $C_{16}H_{12}O_3NaClBr$ $[M+Na]^+$ 388.9556, found 388.9551.

5-Bromo-7-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (155)



155
$C_{16}H_{10}BrClO_4$
MW: 381.61

To a suspension of chalcone **153** (287 mg, 781 µmol, 1.00 eq.) in MeOH (9.25 mL), NaOH (3.00 M, aq., 1.34 mL, 4.02 mmol, 5.15 eq.) was added and cooled to 0 °C. H_2O_2 (35 wt% in H_2O, 257 µL, 3.00 mmol, 3.84 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 16 h. Then, HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate. The suspension was extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOH to give the desired product **155** as a yellow solid (65.0 mg, 170 µmol) in 22% yield.

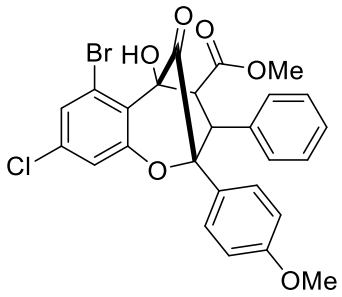
$\mathbf{R}_f$ = 0.31 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 8.18 (dt, $\mathcal{J}$ = 9.9, 2.6 Hz, 2H, 2x Ar*H*), 7.64 (d, $\mathcal{J}$ = 2.0 Hz, 1H, Ar*H*), 7.59 (d, $\mathcal{J}$ = 2.0 Hz, 1H, Ar*H*), 7.16 (s, 1H, O*H*), 7.05 (dt, $\mathcal{J}$ = 9.9, 2.6 Hz, 2H, 2x Ar*H*), 3.90 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 171.7 (q, *C*=O), 161.5 (q, Ar*C*), 156.4 (q, Ar*C*), 144.2 (q, *C*=COH), 138.9 (q, Ar*C*), 137.9 (q, *C*OH), 131.2 (t, Ar*C*H), 129.5 (t, 2x Ar*C*H), 122.8 (q, Ar*C*), 121.2 (q, Ar*C*), 118.2 (t, Ar*C*H), 117.3 (q, Ar*C*), 114.4 (t, 2x Ar*C*H), 55.6 (p, O*C*H_3).

HRMS (EI) *m/z* calcd. for $C_{16}H_{10}ClO_4Br$ $[M]^+$ 379.9451, found 379.9453.

(±)-Methyl (3*S*,4*S*,5*R*)-6-bromo-8-chloro-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E23)

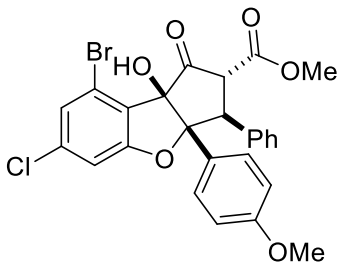


E23
$C_{26}H_{20}BrClO_6$
MW: 543.79

Methyl cinnamate (392 mg, 2.42 mmol, 14.2 eq.) was added to a solution of flavonol **155** (65.0 mg, 170 µmol, 1.00 eq.) in dry chloroform (3.48 mL) and freshly distilled 2,2,2-trifluoroethanol (1.39 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (22 h). Subsequently, the solvent was removed under reduced pressure and the remaining amount of methyl cinnamate was removed by column chromatography (petroleum ether/EtOAc 5:1 → 1:1). Product **E23** was obtained as a mixture of isomers as a yellowish solid (110 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.21 – 0.75 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-8-bromo-6-chloro-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E24)

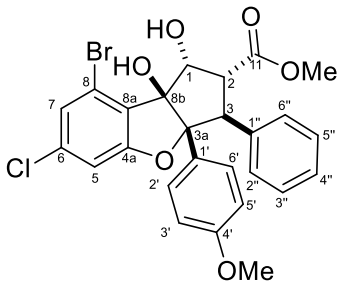


E24
$C_{26}H_{20}BrClO_6$
MW: 543.79

Cycloadduct **E23** (110 mg) was dissolved in MeOH (6.81 mL). Then, NaOMe solution (133 µL, 25 wt% in MeOH, 562 µmol, 3.30 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E24** was obtained as a mixture of isomers as an orange solid (110 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.32 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-bromo-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-157)



(±)-157
$C_{26}H_{22}BrClO_6$
MW: 545.81

A mixture of $(CH_3)_4N(OAc)_3BH$ (288 mg, 1.09 mmol, 6.42 eq.) and freshly distilled AcOH (102 µL, 1.77 mmol, 10.4 eq.) in MeCN (1.50 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E24** (110 mg) in MeCN (1.00 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then performed to obtain the racemic *endo*-product **(±)-157** as a pale-yellow foam (38.0 mg, 69.6 µmol) in 41% yield over 3 steps.

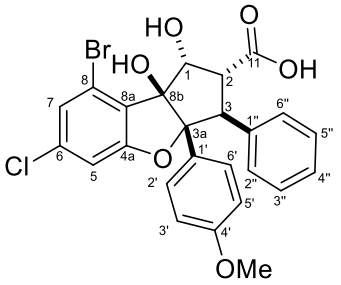
$\mathbf{R}_f$ = 0.55 (CH_2Cl_2/EtOAc 9:1).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.18 (d, J = 1.7 Hz, 1H, *H*-5), 7.15 (d, J = 1.7 Hz, 1H, *H*-7), 7.07 – 7.03 (m, 2H, *H*-2'', *H*-6''), 7.00 – 6.95 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.56 (dt, J = 10.1, 2.6 Hz, 2H, *H*-3', *H*-5'), 5.65 (t, J = 3.0 Hz, 2H, *H*O-1, *H*O-8b), 4.68 (dd, J = 5.9, 4.4 Hz, 1H, *H*-1), 4.41 (d, J = 14.0 Hz, 1H, *H*-3), 4.05 (dd, J = 13.9, 4.3 Hz, 1H, *H*-2), 3.59 (s, 3H, H_3CO-11), 3.57 (s, 3H, H_3CO-4').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.3 (q, *C*-11), 160.8 (q, *C*-4a), 157.6 (q, *C*-4'), 138.0 (q, *C*-1''), 134.4 (q, *C*-6), 128.5 (t, *C*-2', *C*-6'), 128.1 (q, C-1'), 127.9 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 127.2 (q, *C*-8a), 125.8 (t, *C*-4''), 123.7 (t, *C*-7), 120.8 (q, *C*-8), 111.9 (t, *C*-3', *C*-5'), 109.5 (t, *C*-5), 102.4 (q, *C*-3a), 93.9 (q, *C*-8b), 78.0 (t, *C*-1), 54.9 (t, *C*-3), 54.7 (p, H_3CO-4'), 51.7 (t, *C*-2), 51.5 (p, H_3CO-11).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{22}BrClO_6Na$ $[M+Na]^+$ 567.0186 found 567.0172.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-bromo-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxylic acid (E25)



E25
$C_{25}H_{20}BrClO_6$
MW: 531.78

A solution of methyl ester **(±)-157** (34.4 mg, 63.0 µmol, 1.00 eq.) and lithium hydroxide solution (2.00 M in H_2O, 327 µL, 653 µmol, 10.4 eq.) in MeOH (5.08 mL) was heated at 50 °C for 21 h. Subsequently, the solution was allowed to cool to rt, acidified with HCl (1.00 M in H_2O) to pH 1-2 and diluted with CH_2Cl_2 (10.0 mL) and H_2O (10.0 mL). The organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2x 10.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the rocagloic acid **E25** as a yellowish solid (29.5 mg, 55.5 µmol) in 88% yield.

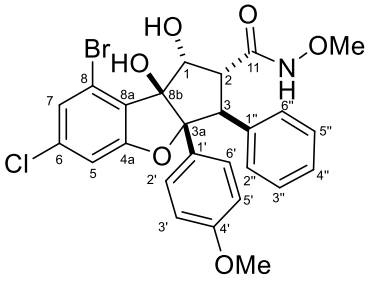
$\mathbf{R}_f$ = 0.56 (EtOAc).

^{1}H-NMR (DMSO-d_6, 600 MHz): δ [ppm] 12.04 (bs, 1H, CO_2H), 7.17 (d, J = 1.6 Hz, 1H, *H*-5), 7.14 (d, J = 1.6 Hz, 1H, *H*-7), 7.07 – 6.94 (m, 7H, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.55 (d, J = 8.9 Hz, 2H, *H*-3', *H*-5'), 5.58 (s, 1H, *H*O-8b), 4.67 (d, J = 3.7 Hz, 1H, *H*-1), 4.39 (d, J = 14.1 Hz, 1H, *H*-3), 3.92 (dd, J = 14.1, 3.6 Hz, 1H, *H*-2), 3.57 (s, 3H, H_3CO-4').

^{13}C-NMR (DMSO-d_6, 150 MHz): δ [ppm] 172.5 (q, *C*-11), 160.9 (q, *C*-4a), 157.5 (q, *C*-4'), 138.6 (q, *C*-1''), 134.2 (q, *C*-6), 128.5 (t, *C*-2', *C*-6'), 128.2 (q, C-1'), 128.1 (t, *C*-3'', *C*-5''), 127.34 (t, *C*-2'', *C*-6''), 127.28 (q, *C*-8a), 125.6 (t, *C*-4''), 123.5 (t, *C*-7), 120.7 (q, *C*-8), 111.8 (t, *C*-3', *C*-5'), 109.4 (t, *C*-5), 102.8 (q, *C*-3a), 94.1 (q, *C*-8b), 77.9 (t, *C*-1), 55.0 (t, *C*-3), 54.7 (p, H_3CO-4'), 51.9 (t, *C*-2).

HRMS (ESI$^-$) *m/z* calcd. for $C_{25}H_{19}ClBrO_6$ $[M-H]^-$ 529.0054, found 529.0065.

(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-Bromo-6-chloro-1,8b-dihydroxy-*N*-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-159)



(±)-159
$C_{26}H_{23}BrClNO_6$
MW: 560.83

To a solution of rocagloic acid **E25** (16.5 mg, 31.0 µmol, 1.00 eq.) in CH_2Cl_2 (2.14 mL) EDC·HCl (8.9 mg, 46.5 µmol, 1.50 eq.), HOBt·H_2O (7.5 mg, 41.9 µmol, 1.35 eq.) and triethylamine (21.6 µL, 155 µmol, 5.00 eq.) were added and was stirred at rt. After 1 h, methoxylamine hydrochloride (13.0 mg, 155 µmol, 5.00 eq.) was added and reaction mixture was stirred for additional 18 h. The reaction was terminated by addition of HCl (1.00 M in H_2O), extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 100:0 ⟶ 95:5). The desired rocagloic amide **(±)-159** was obtained as a colorless solid (4.0 mg, 7.1 µmol) in 23% yield.

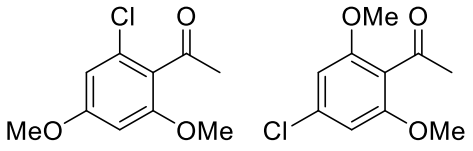
$\mathbf{R}_f$ = 0.30 (CH_2Cl_2/MeOH 95:5).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 11.30 (s, 1H, N*H*OCH$_3$), 7.17 (d, $\mathcal{J}$ = 1.7 Hz, 1H, *H*-5), 7.15 (d, $\mathcal{J}$ = 1.7 Hz, 1H, *H*-7), 7.07 – 7.04 (m, 2H, *H*-2'', *H*-6''), 7.00 – 6.95 (m, 5H, *H*-2', *H*-6', *H*-3'', *H*-4'', *H*-5''), 6.58 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.56 (s, 1H, O*H*-8b), 5.28 (d, $\mathcal{J}$ = 5.3 Hz, 1H, O*H*-1), 4.55 (t, $\mathcal{J}$ = 4.6 Hz, 1H, *H*-1), 4.44 (d, $\mathcal{J}$ = 14.1 Hz, 1H, *H*-3), 3.68 (dd, $\mathcal{J}$ = 14.1, 4.0 Hz, 1H, *H*-2), 3.58 (s, 3H, s, 3H, *H*$_3$CO-4'), 3.53 (s, 3H, NHOC*H*$_3$).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 166.4 (q, *C*-11), 160.8 (q, *C*-4a), 157.6 (q, *C*-4'), 138.0 (q, *C*-1''), 134.3 (q, *C*-6), 128.4 (t, *C*-2', *C*-6'), 128.2 (q, C-1'), 127.9 (t, *C*-3'', *C*-5''), 127.43 (q, *C*-8a), 127.42 (t, *C*-2'', *C*-6''),125.9 (t, *C*-4''), 123.6 (t, *C*-7), 120.9 (q, *C*-8), 111.9 (t, *C*-3', *C*-5'), 109.5 (t, *C*-5), 102.1 (q, *C*-3a), 94.2 (q, *C*-8b), 78.2 (t, *C*-1), 63.2 (p, NHO*C*H$_3$), 54.9 (t, *C*-3), 54.8 (p, H$_3$*C*O-4'), 48.9 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{23}NO_6ClBrNa$ $[M+Na]^+$ 582.0295, found 582.0307.

1-(2-Chloro-4,6-dimethoxyphenyl)ethan-1-one (163) and 1-(4-Chloro-2,6-dimethoxyphenyl)ethan-1-one (164)



163 **164**

$C_{10}H_{11}ClO_3$
MW: 214.65

1-Chloro-3,5-dimethoxybenzene (**161**) (3.05 g, 17.7 mmol, 1.00 eq.) was added to a mixture of $AlCl_3$ (2.83 g, 21.2 mmol, 1.20 eq.) and acetyl chloride (1.32 mL, 18.6 mmol, 1.05 eq.) in CH_2Cl_2 (29.5 mL) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature. Then, H_2O was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with H_2O and NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The isomers were separated by column chromatography (petroleum ether/EtOAc 50:1 ⟶ 5:1) to yield 1-(2-chloro-4,6-dimethoxyphenyl)ethan-1-one (**163**) as a yellowish oil (1.58 g, 7.36 mmol, 42%) and 1-(4-chloro-2,6-dimethoxyphenyl)ethan-1-one (**164**) as a colorless solid (1.08 g, 5.03 mmol, 28%).

1-(2-Chloro-4,6-dimethoxyphenyl)ethan-1-one (163)

$\mathbf{R}_f$ = 0.26 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.49 (d, $\mathcal{J}$ = 2.1 Hz, 1H, Ar*H*), 6.36 (d, $\mathcal{J}$ = 2.1 Hz, 1H, Ar*H*), 3.795 (s, 3H, OC*H*$_3$), 3.786 (s, 3H, OC*H*$_3$), 2.48 (s, 3H, C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 201.3 (q, *C*=O), 161.3 (q, Ar*C*), 158.0 (q, Ar*C*), 131.1 (q, Ar*C*), 123.8 (q, Ar*C*), 106.2 (t, Ar*C*H), 97.6 (t, Ar*C*H), 56.0 (p, O*C*H$_3$), 55.8 (p, O*C*H$_3$), 32.1 (p, *C*H$_3$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{10}H_{11}O_3ClNa$ $[M+Na]^+$ 237.0294, found 237.0296.

1-(4-Chloro-2,6-dimethoxyphenyl)ethan-1-one (164)

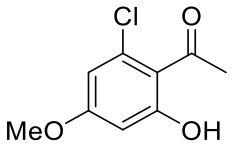
R$_f$ = 0.32 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.56 (s, 2H, 2x Ar*H*), 3.79 (s, 6H, 2x OC*H*$_3$), 2.45 (s, 3H, C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 201.5 (q, *C*=O), 157.1 (q, 2x Ar*C*), 136.3 (q, Ar*C*), 118.9 (q, Ar*C*), 104.9 (t, 2x Ar*C*H), 56.1 (p, 2x O*C*H$_3$), 32.3 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[108]

1-(2-Chloro-6-hydroxy-4-methoxyphenyl)ethan-1-one (167)



167
$C_9H_9ClO_3$
MW: 200.62

A solution of 1-(2-chloro-4,6-dimethoxyphenyl)ethan-1-one (**163**) (1.58 g, 7.36 mmol, 1.00 eq.) in CH_2Cl_2 (7.36 mL) at 0 °C was treated with BBr_3 solution (1.00 M in CH_2Cl_2, 8.10 mL, 8.10 mmol, 1.10 eq.). The orange solution was stirred for 1 h at 0 °C. Subsequently, ice-cold H_2O was added to terminate the reaction. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by recrystallization from EtOH to yield the desired phenol **167** as a greenish solid (979 mg, 4.88 mmol) in 66% yield.

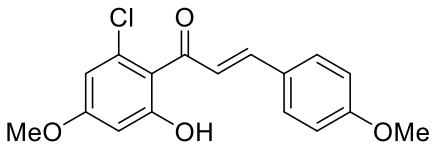
R$_f$ = 0.39 (petroleum ether/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.46 (s, 1H, O*H*), 6.54 (d, $\mathcal{J}$ = 2.6 Hz, 1H, Ar*H*), 6.36 (d, $\mathcal{J}$ = 2.6 Hz, 1H, Ar*H*), 3.82 (s, 3H, OC*H*$_3$), 2.80 (s, 3H, C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 203.7 (q, *C*=O), 167.2 (q, Ar*C*), 164.3 (q, Ar*C*), 136.8 (q, Ar*C*), 113.6 (q, Ar*C*), 111.3 (t, Ar*C*H), 100.5 (t, Ar*C*H), 55.9 (p, O*C*H$_3$), 33.5 (p, *C*H$_3$).

HRMS (ESI$^-$) *m/z* calcd. for $C_9H_8ClO_3$ $[M-H]^-$ 199.0162, found 199.0166.

(*E*)-1-(2-Chloro-6-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (171)



171
$C_{17}H_{15}ClO_4$
MW: 318.75

Acetophenone **167** (979 mg, 4.88 mmol, 1.00 eq.) was added to a solution of NaOEt (996 mg, 14.6 mmol, 3.00 eq.) in EtOH (16.8 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (593 µL, 4.88 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **171** was obtained as a yellow solid (1.49 g, 4.67 mmol) in 96% yield.

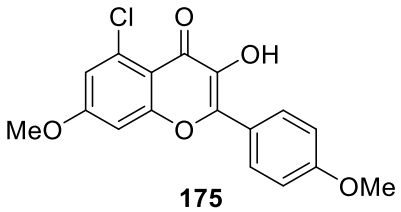
$\mathbf{R}_f$ = 0.31 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 12.60 (s, 1H, O*H*), 7.76 (d, J = 15.5 Hz, 1H, C(O)CH=C*H*), 7.63 (d, J = 15.4 Hz, 1H, C(O)C*H*), 7.59 (dt, J = 8.7, 2.4 Hz, 2H, 2x Ar*H*), 6.95 (dt, J = 8.8, 2.4 Hz, 2H, 2x Ar*H*), 6.58 (d, J = 2.5 Hz, 1H, Ar*H*), 6.41 (d, J = 2.5 Hz, 1H, Ar*H*), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.3 (q, *C*=O), 165.8 (q, Ar*C*), 164.0 (q, Ar*C*), 163.0 (q, Ar*C*), 143.2 (t, C(O)CH=*C*H), 135.6 (q, Ar*C*), 130.6 (t, 2x Ar*C*H), 127.8 (q, Ar*C*), 124.3 (t, C(O)*C*H), 115.0 (q, Ar*C*), 114.6 (t, 2x Ar*C*H), 110.9 (t, Ar*C*H), 100.4 (t, Ar*C*H), 55.9 (p, O*C*H_3), 55.6 (p, O*C*H_3).

HRMS (ESI$^-$) *m/z* calcd. for $C_{17}H_{14}ClO_4$ $[M-H]^-$ 317.0581, found 317.0593.

5-Chloro-3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (175)



175
$C_{17}H_{13}ClO_5$
MW: 332.74

To a suspension of chalcone **171** (1.49 g, 4.67 mmol, 1.00 eq.) in MeOH (40.2 mL), NaOH (3.00 M, aq., 6.03 mL, 18.1 mmol, 3.87 eq.) was added and cooled to 0 °C. H_2O_2 (30 wt% in H_2O, 1.52 mL, 15.0 mmol, 3.20 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 20 h. Then, HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate. The suspension was then extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOH to give the desired product **175** as a yellowish solid (192 mg, 595 µmol) in 13% yield.

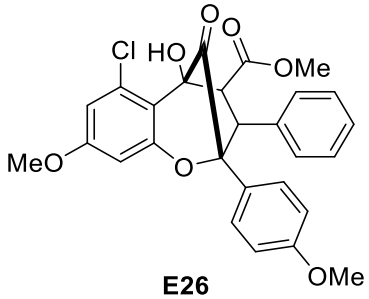
$\mathbf{R}_f$ = 0.33 (petroleum ether/EtOAc 3:2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.16 (dt, $\mathcal{J}$ = 9.1, 2.5 Hz, 2H, 2x Ar*H*), 7.20 (s, 1H, O*H*), 7.03 (dt, $\mathcal{J}$ = 9.1, 2.4 Hz, 2H, 2x Ar*H*), 6.98 (d, $\mathcal{J}$ = 2.4 Hz, 1H, Ar*H*), 6.87 (d, $\mathcal{J}$ = 2.5 Hz, 1H, Ar*H*), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 171.8 (q, *C*=O), 162.7 (q, Ar*C*), 161.1 (q, Ar*C*), 158.3 (q, Ar*C*), 143.3 (q, *C*=COH), 137.6 (q, *C*OH), 134.4 (q, Ar*C*), 129.2 (t, 2x Ar*C*H), 123.3 (q, Ar*C*), 116.9 (t, Ar*C*H), 114.2 (t, 2x Ar*C*H), 112.0 (q, Ar*C*), 99.8 (t, Ar*C*H), 56.2 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$).

HRMS (CI$^+$) *m/z* calcd. for $C_{17}H_{14}ClO_5$ $[M+H]^+$ 333.0530, found 333.0514.

(±)-Methyl (3*S*,4*S*,5*R*)-6-chloro-5-hydroxy-8-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E26)

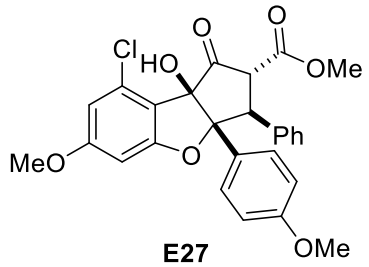


E26
$C_{27}H_{23}ClO_7$
MW: 494.92

Methyl cinnamate (1.37 g, 8.45 mmol, 14.2 eq.) was added to a solution of flavonol **175** (192 mg, 595 µmol, 1.00 eq.) in dry chloroform (11.7 mL) and freshly distilled 2,2,2-trifluoroethanol (4.96 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 9:1 → 1:1). Product **E26** was obtained as a mixture of isomers as a yellowish solid (289 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.19 – 0.67 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-8-chloro-8b-hydroxy-6-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E27)



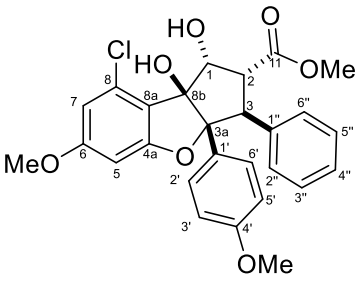
E27
$C_{27}H_{23}ClO_7$
MW: 494.92

Cycloadduct **E26** (289 mg, 584 µmol, 1.00 eq.) was dissolved in MeOH (21.6 mL). Then NaOMe solution (315 µL, 25 wt% in MeOH, 1.90 mmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq.,

sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Product **E27** was obtained as a mixture of isomers as a yellow foam (289 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.56 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-chloro-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-179)



(±)-179
$C_{27}H_{25}ClO_7$
MW: 496.94

A mixture of $(CH_3)_4N(OAc)_3BH$ (986 mg, 3.75 mmol, 6.42 eq.) and freshly distilled AcOH (348 µL, 6.08 mmol, 10.4 eq.) in MeCN (15.2 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E27** (289 mg, 584 µmol, 1.00 eq.) in MeCN (10.1 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then performed to obtain the racemic *endo*-product **(±)-179** as a colorless foam (160 mg, 323 µmol) in 54% yield over 3 steps.

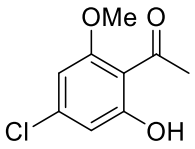
$\mathbf{R}_f$ = 0.46 (CH_2Cl_2/EtOAc 19:1).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.07 – 6.94 (m, 7H, *H*-7, *H*-2', H-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.61 (d, $\mathcal{J}$ = 2.1 Hz, 1H, *H*-5), 6.56 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 6.49 (d, $\mathcal{J}$ = 2.1 Hz, 1H, *H*-7), 5.56 (d, $\mathcal{J}$ = 6.1 Hz, 1H, O*H*-1), 5.43 (s, 1H, O*H*-8b), 4.65 (dd, $\mathcal{J}$ = 5.6, 4.9 Hz, 1H, *H*-1), 4.34 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 4.02 (dd, $\mathcal{J}$ = 14.0, 4.5 Hz, 1H, *H*-2), 3.78 (s, 3H, H_3CO-8), 3.58 (s, 6H, H_3CO-11, H_3CO-4'').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.4 (q, *C*-11), 161.6 (q, *C*-6), 161.1 (q, *C*-4a), 157.5 (q, *C*-4'), 138.3 (q, *C*-1''), 131.9 (q, *C*-8), 128.6 (q, *C*-1'), 128.6 (t, *C*-2', *C*-6'), 127.8 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 125.8 (t, *C*-4''), 118.5 (q, *C*-8a), 111.8 (t, *C*-3', *C*-5'), 107.6 (t, *C*-7), 101.9 (q, *C*-3a), 94.8 (t, *C*-5), 93.6 (q, *C*-8b), 78.2 (t, *C*-1), 55.9 (p, H_3CO-6), 54.9 (t, *C*-3), 54.7 (p, H_3CO-4'), 51.7 (t, *C*-2), 51.5 (p, H_3CO-11).

HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{25}ClO_7Na$ $[M+Na]^+$ 519.1187 found 519.1182.

1-(4-Chloro-2-hydroxy-6-methoxyphenyl)ethan-1-one (168)



168
$C_9H_9ClO_3$
MW: 200.62

A solution of 1-(4-chloro-2,6-dimethoxyphenyl)ethan-1-one (**164**) (1.08 g, 5.03 mmol, 1.00 eq.) in CH_2Cl_2 (5.00 mL) at 0 °C was treated with BBr_3 solution (1.00 M in CH_2Cl_2, 5.53 mL, 5.53 mmol, 1.10 eq.). The orange solution was stirred for 1 h at 0 °C. Subsequently, ice-cold H_2O was added to termiante the reaction. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by recrystallization from EtOH to yield the desired phenol **168** as a yellowish solid (814 mg, 4.06 mmol) in 81% yield.

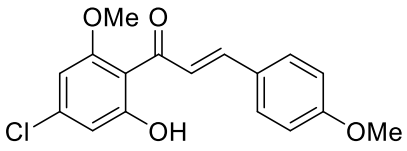
$\mathbf{R}_f$ = 0.37 (petroleum ether/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.49 (s, 1H, O*H*), 6.60 (d, J = 2.0 Hz, 1H, Ar*H*), 6.38 (d, J = 2.0 Hz, 1H, Ar*H*), 3.90 (s, 3H, OCH_3), 2.65 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.6 (q, *C*=O), 165.4 (q, Ar*C*), 162.0 (q, Ar*C*), 142.3 (q, Ar*C*), 111.3 (t, Ar*C*H), 109.9 (q, Ar*C*), 102.6 (t, Ar*C*H), 56.1 (p, O*C*H_3), 33.6 (p, *C*H_3).

The analytical data are consistent with those reported in the literature.[108]

(*E*)-1-(4-Chloro-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (172)



172
$C_{17}H_{15}ClO_4$
MW: 318.75

Acetophenone **168** (814 mg, 4.06 mmol, 1.00 eq.) was added to a solution of NaOEt (828 mg, 12.2 mmol, 3.00 eq.) in EtOH (14.0 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (493 µL, 4.05 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **172** was obtained as a yellow solid (1.22 g, 3.92 mmol) in 94% yield.

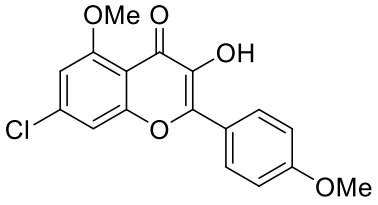
$\mathbf{R}_f$ = 0.28 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.62 (s, 1H, O*H*), 7.83 (d, J = 15.6 Hz, 1H, C(O)CH=C*H*), 7.72 (d, J = 15.5 Hz, 1H, C(O)C*H*), 7.58 (dt, J = 8.8, 2.4 Hz, 2H, 2x Ar*H*), 6.95 (dt, J = 8.8, 2.4 Hz, 2H, 2x Ar*H*), 6.58 (d, J = 2.5 Hz, 1H, Ar*H*), 6.41 (d, J = 2.5 Hz, 1H, Ar*H*), 3.96 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.7 (q, *C*=O), 165.7 (q, Ar*C*), 161.9 (q, Ar*C*), 161.5 (q, Ar*C*), 144.0 (t, C(O)CH=*C*H), 141.8 (q, Ar*C*), 130.5 (t, 2x Ar*C*H), 128.0 (q, Ar*C*), 124.7 (t, C(O)*C*H), 114.7 (t, 2x Ar*C*H), 111.5 (t, Ar*C*H), 110.6 (q, Ar*C*), 102.9 (t, Ar*C*H), 56.4 (p, O*C*H$_3$), 55.6 (p, O*C*H$_3$).

HRMS (ESI$^-$) *m/z* calcd. for $C_{17}H_{14}ClO_4$ $[M-H]^-$ 317.0578, found 317.0593.

7-Chloro-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (176)



176
$C_{17}H_{13}ClO_5$
MW: 332.74

To a suspension of chalcone **172** (935 mg, 2.93 mmol, 1.00 eq.) in MeOH (25.2 mL), NaOH (3.00 M, aq., 3.78 mL, 11.4 mmol, 3.87 eq.) was added and cooled to 0 °C. H_2O_2 (30 wt% in H_2O, 957 µL, 9.39 mmol, 3.20 eq.) was then added dropwise and the solution was stirred at 0 °C for 3 h. Subsequently, the cooling bath was removed and the mixture was stirred for another 20 h. Then, HCl (10 wt% in H_2O) was added leading to the formation of a yellow precipitate. The suspension was then extracted with CH_2Cl_2 (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOH to give the desired product **176** as a bright orange solid (305 mg, 945 µmol) in 32% yield.

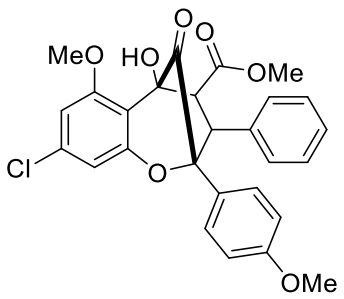
R$_f$ = 0.21 (petroleum ether/EtOAc 3:2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.16 (d, $\mathcal{J}$ = 8.7 Hz, 2H, 2x Ar*H*), 7.28 (s, 1H, O*H*), 7.17 (s, 1H, Ar*H*), 7.03 (d, $\mathcal{J}$ = 8.8 Hz, 2H, 2x Ar*H*), 6.75 (s, 1H, Ar*H*), 4.02 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.1 (q, *C*=O), 161.1 (q, Ar*C*), 160.1 (q, Ar*C*), 157.1 (q, Ar*C*), 143.1 (q, *C*=COH), 139.9 (q, Ar*C*), 138.0 (q, *C*OH), 129.3 (t, 2x Ar*C*H), 123.1 (q, Ar*C*), 114.2 (t, 2x Ar*C*H), 110.6 (t, Ar*C*H), 110.2 (q, Ar*C*), 106.5 (t, Ar*C*H), 56.9 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$).

HRMS (CI$^+$) *m/z* calcd. for $C_{17}H_{14}ClO_5$ $[M+H]^+$ 333.0530, found 333.0515.

(±)-Methyl (3*S*,4*S*,5*R*)-8-chloro-5-hydroxy-6-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E28)

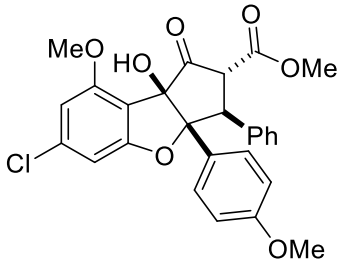


E28
$C_{27}H_{23}ClO_7$
MW: 494.92

Methyl cinnamate (2.18 g, 13.4 mmol, 14.2 eq.) was added to a solution of flavonol **176** (305 mg, 945 µmol, 1.00 eq.) in dry chloroform (18.5 mL) and freshly distilled 2,2,2-trifluoroethanol (7.88 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 9:1 → 1:1). Product **E28** was obtained as a mixture of isomers as a yellowish solid (421 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.11 – 0.54 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-6-chloro-8b-hydroxy-8-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E29)

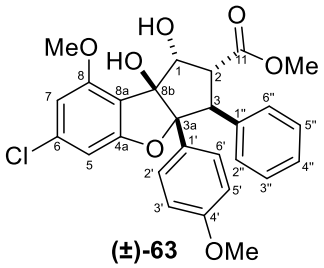


E29
$C_{27}H_{23}ClO_7$
MW: 494.92

Cycloadduct **E28** (421 mg, 850 µmol, 1.00 eq.) was dissolved in MeOH (31.5 mL). Then NaOMe solution (459 µL, 25 wt% in MeOH, 2.76 mmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E29** was obtained as a mixture of isomers as a yellow foam (421 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.47 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-63)



(±)-63
$C_{27}H_{25}ClO_7$
MW: 496.94

A mixture of $(CH_3)_4N(OAc)_3BH$ (1.44 g, 5.45 mmol, 6.42 eq.) and freshly distilled AcOH (506 µL, 8.84 mmol, 10.4 eq.) in MeCN (22.1 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E29** (421 mg, 850 µmol, 1.00 eq.) in MeCN (14.7 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then performed to obtain the racemic *endo*-product **(±)-63** as a yellowish foam (225 mg, 452 µmol) in 48% yield over 3 steps.

$\mathbf{R}_f$ = 0.31 (CH_2Cl_2/EtOAc 19:1).

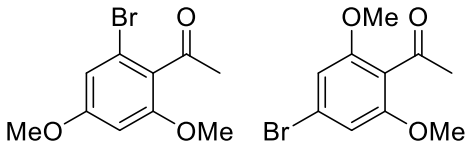
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.06 – 6.95 (m, 5H, *H*-7, *H*-2', H-6', *H*-2'', *H*-4'', *H*-6''), 6.91 (d, $\mathcal{J}$ = 7.3 Hz, 2H, *H*-3'', *H*-5''), 6.74 (d, $\mathcal{J}$ = 1.6 Hz, 1H, *H*-7), 6.59 (d, $\mathcal{J}$ = 1.5 Hz, 1H, *H*-5), 6.57 (d, $\mathcal{J}$ = 9.0 Hz, 2H, *H*-3', *H*-5'), 5.33 – 5.32 (m, 2H, O*H*-1, O*H*-8b), 4.69 (t, $\mathcal{J}$ = 5.2 Hz, 1H, *H*-1), 4.22 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 3.97 (dd, $\mathcal{J}$ = 14.0, 5.1 Hz, 1H, *H*-2), 3.75 (s, 3H, H_3CO-8), 3.58 (s, 3H, H_3CO-4''), 3.55 (s, 3H, H_3CO-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.4 (q, *C*-11), 160.2 (q, *C*-4a), 158.1 (q, *C*-8), 157.6 (q, *C*-4'), 138.2 (q, *C*-1''), 134.8 (q, *C*-6), 128.7 (t, *C*-2', *C*-6'), 128.3 (q, *C*-1'), 127.8 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 125.9 (t, *C*-4''), 114.8 (q, *C*-8a), 111.9 (t, *C*-3', *C*-5'), 104.5 (t, *C*-5), 103.4 (t, *C*-7), 101.8 (q, *C*-3a), 93.2 (q, *C*-8b), 78.6 (t, *C*-1), 55.9 (p, H_3CO-8), 54.85 (t, *C*-3), 54.81 (p, H_3CO-4'), 51.5 (p, H_3CO-11), 51.3 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{25}ClO_7Na$ $[M+Na]^+$ 519.1187 found 519.1173.

The analytical data are consistent with those reported in the literature.[66]

1-(2-Bromo-4,6-dimethoxyphenyl)ethan-1-one (165) and 1-(4-Bromo-2,6-dimethoxyphenyl)ethan-1-one (166)



165 **166**

$C_{10}H_{11}BrO_3$
MW: 259.10

1-Bromo-3,5-dimethoxybenzene (**162**) (3.00 g, 13.8 mmol, 1.00 eq.) was added to a mixture of $AlCl_3$ (2.21 g, 16.6 mmol, 1.20 eq.) and acetyl chloride (1.14 mL, 14.5 mmol, 1.05 eq.) in CH_2Cl_2 (23.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature. Then, H_2O was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with H_2O and NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The isomers were separated by column chromatography (petroleum ether/EtOAc 50:1 ⟶ 5:1) to yield 1-(2-bromo-4,6-dimethoxyphenyl)ethan-1-one (**165**) as a yellowish oil (575 mg, 2.22 mmol, 16%) and 1-(4-bromo-2,6-dimethoxyphenyl)ethan-1-one (**166**) as a colorless solid (1.12 g, 4.30 mmol, 31%)

1-(2-Bromo-4,6-dimethoxyphenyl)ethan-1-one (165)

$\mathbf{R}_f$ = 0.29 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.67 (d, J = 2.1 Hz, 1H, Ar*H*), 6.40 (d, J = 2.1 Hz, 1H, Ar*H*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.49 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 201.2 (q, *C*=O), 161.4 (q, Ar*C*), 157.9 (q, Ar*C*), 125.9 (q, Ar*C*), 118.8 (q, Ar*C*), 109.1 (t, Ar*C*H), 98.3 (t, Ar*C*H), 56.0 (p, O*C*H$_3$), 55.8 (p, O*C*H$_3$), 31.9 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[233]

1-(4-Bromo-2,6-dimethoxyphenyl)ethan-1-one (166)

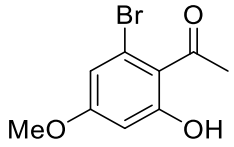
$\mathbf{R}_f$ = 0.39 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.71 (s, 2H, 2x Ar*H*), 3.79 (s, 6H, 2x OCH_3), 2.44 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 201.7 (q, *C*=O), 157.3 (q, 2x Ar*C*), 124.2 (q, Ar*C*), 119.6 (q, Ar*C*), 108.0 (t, 2x Ar*C*H), 56.3 (p, 2x O*C*H$_3$), 32.4 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[108]

1-(2-Bromo-6-hydroxy-4-methoxyphenyl)ethan-1-one (169)



169
$C_9H_9BrO_3$
MW: 245.07

A solution of 1-(2-chloro-4,6-dimethoxyphenyl)ethan-1-one (**165**) (575 mg, 2.22 mmol, 1.00 eq.) in CH_2Cl_2 (2.22 mL) at 0 °C was treated with BBr_3 solution (1.00 M in CH_2Cl_2, 2.44 mL, 2.44 mmol, 1.10 eq.). The orange solution was stirred for 1 h at 0 °C. Subsequently, ice-cold H_2O was added to terminate the reaction. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by recrystallization from EtOH to yield the desired phenol **169** as a light brown solid (430 mg, 1.75 mmol) in 79% yield.

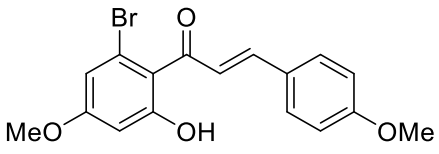
$\mathbf{R}_f$ = 0.35 (petroleum ether/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.25 (s, 1H, O*H*), 6.81 (d, J = 2.6 Hz, 1H, Ar*H*), 6.40 (d, J = 2.6 Hz, 1H, Ar*H*), 3.82 (s, 3H, OCH_3), 2.85 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.2 (q, *C*=O), 166.9 (q, Ar*C*), 164.2 (q, Ar*C*), 124.8 (q, Ar*C*), 115.5 (q, Ar*C*), 115.3 (t, Ar*C*H), 101.0 (t, Ar*C*H), 55.9 (p, O*C*H$_3$), 33.5 (p, *C*H$_3$).

HRMS (ESI$^-$) *m/z* calcd. for $C_9H_8BrO_3$ $[M–H]^-$ 242.9657, found 242.9654.

(*E*)-1-(2-Bromo-6-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (173)



173
$C_{17}H_{15}BrO_4$
MW: 363.21

Acetophenone **169** (430 mg, 1.75 mmol, 1.00 eq.) was added to a solution of NaOEt (358 mg, 5.26 mmol, 3.00 eq.) in EtOH (6.05 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (213 µL, 1.75 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **173** was obtained as a yellow solid (617 mg, 1.70 mmol) in 97% yield.

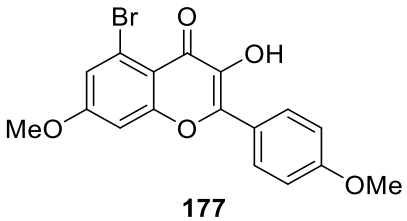
$\mathbf{R}_f$ = 0.34 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 12.14 (s, 1H, O*H*), 7.74 (d, J = 15.6 Hz, 1H, C(O)CH=C*H*), 7.62 (d, J = 15.4 Hz, 1H, C(O)C*H*), 7.59 (d, J = 8.6, 2H, 2x Ar*H*), 6.94 (dt, J = 8.8 Hz, 2H, 2x Ar*H*), 6.82 (d, J = 2.6 Hz, 1H, Ar*H*), 6.45 (d, J = 2.6 Hz, 1H, Ar*H*), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.9 (q, *C*=O), 165.1 (q, Ar*C*), 164.0 (q, Ar*C*), 162.0 (q, Ar*C*), 142.7 (t, C(O)CH=*C*H), 130.6 (t, 2x Ar*C*H), 127.9 (q, Ar*C*), 124.3 (t, C(O)*C*H), 123.6 (q, Ar*C*), 117.0 (q, Ar*C*), 114.7 (t, 2x Ar*C*H), 114.5 (t, Ar*C*H), 100.9 (t, Ar*C*H), 55.9 (p, O*C*H_3), 55.6 (p, O*C*H_3).

HRMS (ESI$^-$) *m/z* calcd. for $C_{17}H_{14}BrO_4$ $[M-H]^-$ 361.0075, found 361.0071.

5-Bromo-3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (177)



177
$C_{17}H_{13}BrO_5$
MW: 377.19

To a suspension of chalcone **173** (617 mg, 1.70 mmol, 1.00 eq.) in MeOH (14.6 mL), NaOH (3.00 M, aq., 2.19 mL, 6.57 mmol, 3.87 eq.) was added and the mixture was stirred for 1 h at rt. Subsequently, the solution was cooled to 0 °C, H_2O_2 (30 wt% in H_2O, 554 µL, 5.44 mmol, 3.20 eq.) was added dropwise. After 3 h stirring at the same temperature, the cooling bath was removed and the mixture was stirred for another 20 h. HCl (10 wt% in H_2O) was then added leading to the formation of a yellow precipitate. The suspension was then extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOH to give the desired product **177** as a bright yellow solid (135 mg, 358 µmol) in 21% yield.

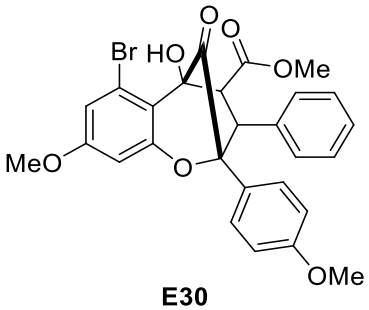
$\mathbf{R}_f$ = 0.52 (petroleum ether/EtOAc 1:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.18 (d, $\mathcal{J}$ = 8.5 Hz, 2H, 2x Ar*H*), 7.26 (s, 1H, O*H*), 7.19 (s, 1H, Ar*H*)), 7.04 (d, $\mathcal{J}$ = 8.2 Hz, 2H, 2x Ar*H*), 6.94 (s, 1H, Ar*H*), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 171.8 (q, *C*=O), 162.8 (q, Ar*C*), 161.1 (q, Ar*C*), 158.1 (q, Ar*C*), 143.3 (q, *C*=COH), 137.3 (q, *C*OH), 129.2 (t, 2x Ar*C*H), 123.3 (q, Ar*C*), 121.1 (q, Ar*C*), 120.7 (t, Ar*C*H), 114.2 (t, 2x Ar*C*H), 112.6 (q, Ar*C*), 100.5 (t, Ar*C*H), 56.2 (p, O*C*H$_3$), 55.6 (p, O*C*H$_3$).

HRMS (EI) *m/z* calcd. for $C_{17}H_{13}BrO_5$ $[M]^+$ 375.9946, found 375.9948.

(±)-Methyl (3*S*,4*S*,5*R*)-6-bromo-5-hydroxy-8-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]oxepine-4-carboxylate (E30)

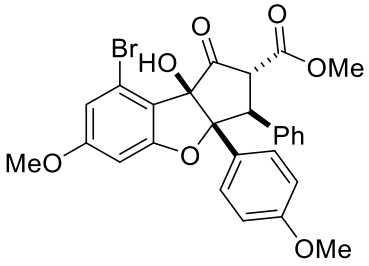


E30
$C_{27}H_{23}BrO_7$
MW: 539.38

Methyl cinnamate (1.08 g, 6.63 mmol, 14.2 eq.) was added to a solution of flavonol **177** (176 mg, 467 µmol, 1.00 eq.) in dry chloroform (9.15 mL) and freshly distilled 2,2,2-trifluoroethanol (3.89 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 9:1 ⟶ 1:1). Product **E30** was obtained as a mixture of isomers as a yellowish solid (252 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.26 − 0.65 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-8-bromo-8b-hydroxy-6-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E31)



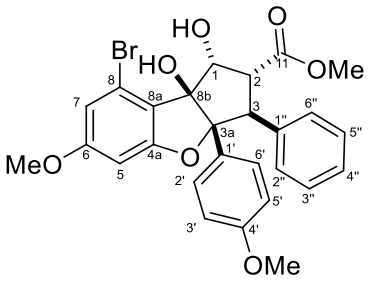
E31
$C_{27}H_{23}BrO_7$
MW: 539.38

Cycloadduct **E30** (252 mg, 467 µmol, 1.00 eq.) was dissolved in MeOH (17.3 mL). Then NaOMe solution (252 µL, 25 wt% in MeOH, 1.52 mmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq.,

sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E31** was obtained as a mixture of isomers as a yellow foam (233 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.52 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-bromo-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-180)



(±)-180
$C_{27}H_{25}BrO_7$
MW: 541.39

A mixture of $(CH_3)_4N(OAc)_3BH$ (730 mg, 2.77 mmol, 6.42 eq.) and freshly distilled AcOH (257 µL, 4.50 mmol, 10.4 eq.) in MeCN (11.2 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E31** (233 mg, 432 µmol, 1.00 eq.) in MeCN (14.7 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then performed to obtain the racemic *endo*-product **(±)-180** as a yellow foam (92.4 mg, 171 µmol) in 37% yield over 3 steps.

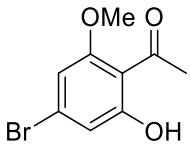
$\mathbf{R}_f$ = 0.41 (CH_2Cl_2/EtOAc 19:1).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.07 – 6.94 (m, 7H, *H*-7, *H*-2', H-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.65 (d, J = 2.1 Hz, 1H, *H*-5), 6.63 (d, J = 2.1 Hz, 1H, *H*-7), 6.55 (d, J = 8.8 Hz, 2H, *H*-3', *H*-5'), 5.48 (d, J = 5.9 Hz, 1H, O*H*-1), 5.38 (s, 1H, O*H*-8b), 4.65 (dd, J = 5.6, 4.5 Hz, 1H, *H*-1), 4.39 (d, J = 13.9 Hz, 1H, *H*-3), 4.02 (dd, J = 13.9, 4.4 Hz, 1H, *H*-2), 3.78 (s, 3H, H_3CO-8), 3.59 (s, 3H, H_3CO-11), 3.58 (s, 3H, H_3CO-4').

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.4 (q, *C*-11), 161.6 (q, *C*-6), 161.3 (q, *C*-4a), 157.5 (q, *C*-4'), 138.3 (q, *C*-1''), 128.7 (q, *C*-1'), 128.6 (t, *C*-2', *C*-6'), 127.8 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 125.7 (t, *C*-4''), 120.3 (q, *C*-8), 120.1 (q, *C*-8a), 111.8 (t, *C*-3', *C*-5'), 110.5 (t, *C*-7), 102.0 (q, *C*-3a), 95.2 (t, *C*-5), 94.0 (q, *C*-8b), 78.1 (t, *C*-1), 55.8 (p, H_3*C*O-8), 54.8 (t, *C*-3), 54.7 (p, H_3*C*O-4'), 51.7 (t, *C*-2), 51.5 (p, H_3*C*O-11).

HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{25}BrO_7Na$ $[M+Na]^+$ 563.0681 found 563.0663.

1-(4-Bromo-2-hydroxy-6-methoxyphenyl)ethan-1-one (170)



170
$C_9H_9BrO_3$
MW: 245.07

A solution of 1-(4-bromo-2,6-dimethoxyphenyl)ethan-1-one (**166**) (1.12 g, 4.30 mmol, 1.00 eq.) in CH_2Cl_2 (4.30 mL) at 0 °C was treated with BBr_3 solution (1.00 M in CH_2Cl_2, 4.73 mL, 4.73 mmol, 1.10 eq.). The orange solution was stirred for 1 h at 0 °C. Subsequently, ice-cold H_2O was added to terminate the reaction. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with NaCl solution (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by recrystallization from EtOH to yield the desired phenol **170** as a yellowish solid (926 mg, 3.78 mmol) in 88% yield.

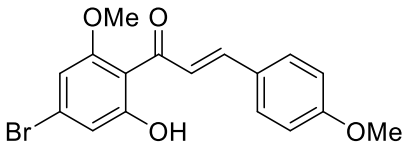
$\mathbf{R}_f$ = 0.36 (petroleum ether/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.44 (s, 1H, O*H*), 6.77 (d, $\mathcal{J}$ = 1.8 Hz, 1H, Ar*H*), 6.54 (d, $\mathcal{J}$ = 1.7 Hz, 1H, Ar*H*), 3.90 (s, 3H, OCH_3), 2.65 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.8 (q, *C*=O), 165.2 (q, Ar*C*), 161.8 (q, Ar*C*), 130.8 (q, Ar*C*), 114.4 (t, Ar*C*H), 110.2 (q, Ar*C*), 105.5 (t, Ar*C*H), 56.2 (p, O*C*H$_3$), 33.7 (p, *C*H$_3$).

The analytical data are consistent with those reported in the literature.[108]

(*E*)-1-(4-Bromo-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (174)



174
$C_{17}H_{15}BrO_4$
MW: 363.21

Acetophenone **170** (926 mg, 3.78 mmol, 1.00 eq.) was added to a solution of NaOEt (771 mg, 11.3 mmol, 3.00 eq.) in EtOH (13.0 mL). After stirring for 1 h at rt, 4-methoxybenzaldehyde (459 µL, 3.78 mmol, 1.00 eq.) was added and the reaction mixture was stirred overnight. The resulting yellow suspension was poured into H_2O and acidified to pH 1 with HCl (10 wt% in H_2O). The yellow precipitate was filtered, washed with H_2O and dried under reduced pressure. The desired compound **174** was obtained as a yellow solid (970 mg, 2.67 mmol) in 71% yield.

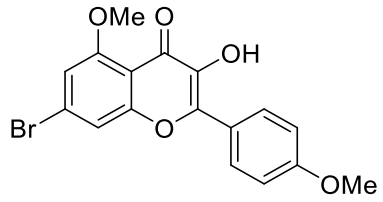
$\mathbf{R}_f$ = 0.29 (petroleum ether/EtOAc 4:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.56 (s, 1H, O*H*), 7.83 (d, $\mathcal{J}$ = 15.5 Hz, 1H, C(O)CH=C*H*), 7.71 (d, $\mathcal{J}$ = 15.5 Hz, 1H, C(O)C*H*), 7.57 (d, $\mathcal{J}$ = 8.7 Hz, 2H, 2x Ar*H*), 6.94 (dt, $\mathcal{J}$ = 8.7 Hz, 2H, 2x Ar*H*), 6.81 (d, $\mathcal{J}$ = 1.8 Hz, 1H, Ar*H*), 6.58 (d, $\mathcal{J}$ = 1.7 Hz, 1H, Ar*H*), 3.95 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 193.9 (q, *C*=O), 165.5 (q, Ar*C*), 161.9 (q, Ar*C*), 161.2 (q, Ar*C*), 144.0 (t, C(O)CH=*C*H), 130.5 (t, 2x Ar*C*H), 130.2 (q, Ar*C*), 128.0 (q, Ar*C*), 124.7 (t, C(O)*C*H), 114.61 (t, Ar*C*H), 114.59 (t, 2x Ar*C*H), 110.9 (q, Ar*C*), 105.8 (t, Ar*C*H), 56.4 (p, O*C*H$_3$), 55.6 (p, O*C*H$_3$).

HRMS (ESI$^-$) *m/z* calcd. for $C_{17}H_{14}BrO_4$ $[M-H]^-$ 361.0075, found 361.0076.

7-Bromo-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (178)



178
$C_{17}H_{13}BrO_5$
MW: 377.19

To a suspension of chalcone **174** (960 mg, 2.64 mmol, 1.00 eq.) in MeOH (22.7 mL), NaOH (3.00 M, aq., 3.41 mL, 10.2 mmol, 3.87 eq.) was added and the mixture was stirred for 1 h at rt. Subsequently, the solution was cooled to 0 °C, H_2O_2 (30 wt% in H_2O, 862 µL, 8.46 mmol, 3.20 eq.) was added dropwise. After 3 h stirring at the same temperature, the cooling bath was removed and the mixture was stirred for another 20 h. HCl (10 wt% in H_2O) was then added leading to the formation of a yellow precipitate. The suspension was then extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from EtOH to give the desired product **178** as a bright yellow solid (396 mg, 1.05 mmol) in 40% yield.

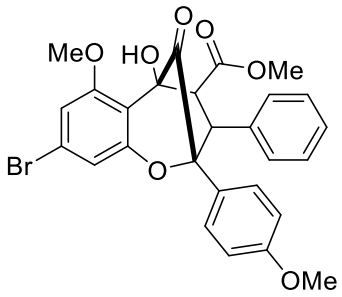
R$_f$ = 0.25 (petroleum ether/EtOAc 1:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.15 (d, J = 9.1 Hz, 2H, 2x Ar*H*), 7.33 (d, J = 1.5 Hz, 1H, Ar*H*), 7.28 (s, 1H, O*H*), 7.02 (d, J = 9.1 Hz, 2H, 2x Ar*H*), 6.89 (d, J = 1.4 Hz, 1H, Ar*H*), 4.01 (s, 3H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.1 (q, *C*=O), 161.1 (q, Ar*C*), 159.9 (q, Ar*C*), 157.0 (q, Ar*C*), 143.1 (q, *C*=COH), 138.1 (q, *C*OH), 129.3 (t, 2x Ar*C*H), 127.9 (q, Ar*C*), 123.1 (q, Ar*C*), 114.2 (t, 2x Ar*C*H), 113.7 (t, Ar*C*H), 110.5 (q, Ar*C*), 109.3 (t, Ar*C*H), 56.9 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$).

HRMS (EI) *m/z* calcd. for $C_{17}H_{13}BrO_5$ $[M]^+$ 375.9946, found 375.9938.

(±)-Methyl (3*S*,4*S*,5*R*)-8-bromo-5-hydroxy-6-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E32)

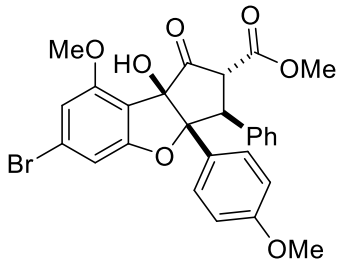


E32
$C_{27}H_{23}BrO_7$
MW: 539.38

Methyl cinnamate (2.20 g, 13.6 mmol, 14.2 eq.) was added to a solution of flavonol **178** (360 mg, 954 µmol, 1.00 eq.) in dry chloroform (18.7 mL) and freshly distilled 2,2,2-trifluoroethanol (7.95 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 9:1 → 1:1). Product **E32** was obtained as a mixture of isomers as a yellowish solid (498 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.23 – 0.62 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-6-bromo-8b-hydroxy-8-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E33)

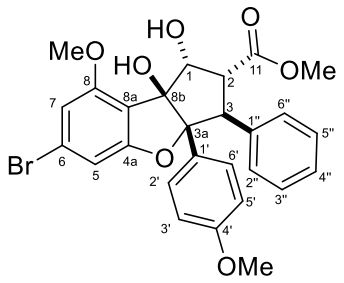


E33
$C_{27}H_{23}BrO_7$
MW: 539.38

Cycloadduct **E32** (498 mg, 923 µmol, 1.00 eq.) was dissolved in MeOH (34.2 mL). Then NaOMe solution (499 µL, 25 wt% in MeOH, 3.00 mmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E33** was obtained as a mixture of isomers as a yellow solid (451 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.30 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-bromo-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-181)



(±)-181
$C_{27}H_{25}BrO_7$
MW: 541.39

A mixture of $(CH_3)_4N(OAc)_3BH$ (1.41 g, 5.37 mmol, 6.42 eq.) and freshly distilled AcOH (498 µL, 8.70 mmol, 10.4 eq.) in MeCN (21.7 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E33** (451 mg, 836 µmol, 1.00 eq.) in MeCN (14.4 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 1:0 ⟶ 9:1) was then performed to obtain the racemic *endo*-product **(±)-181** as a yellow foam (228 mg, 421 µmol) in 44% yield over 3 steps.

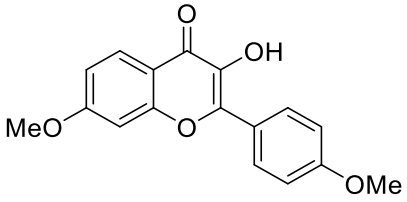
$\mathbf{R}_f$ = 0.30 (CH_2Cl_2/EtOAc 19:1).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.07 – 6.96 (m, 5H, *H*-2', H-6', *H*-2'', *H*-4'', *H*-6''), 6.91 (d, $\mathcal{J}$ = 7.4 Hz, 2H, *H*-3'', *H*-5''), 6.87 (d, $\mathcal{J}$ = 1.2 Hz, 1H, *H*-5), 6.71 (d, $\mathcal{J}$ = 1.3 Hz, 1H, *H*-7), 6.57 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-3', *H*-5'), 5.32 – 5.31 (m, 2H, O*H*-1, O*H*-8b), 4.66 (t, $\mathcal{J}$ = 5.1 Hz, 1H, *H*-1), 4.22 (d, $\mathcal{J}$ = 14.0 Hz, 1H, *H*-3), 3.97 (dd, $\mathcal{J}$ = 14.0, 5.0 Hz, 1H, *H*-2), 3.76 (s, 3H, H_3CO-8), 3.59 (s, 3H, H_3CO-4'), 3.56 (s, 3H, H_3CO-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.3 (q, *C*-11), 160.4 (q, *C*-4a), 158.2 (q, *C*-8), 157.5 (q, *C*-4'), 138.1 (q, *C*-1''), 128.6 (t, *C*-2', *C*-6'), 128.2 (q, *C*-1'), 127.8 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 125.8 (t, *C*-4''), 122.8 (q, *C*-6), 115.2 (q, *C*-8a), 111.8 (t, *C*-3', *C*-5'), 107.2 (t, *C*-7), 106.3 (t, *C*-5), 101.7 (q, *C*-3a), 93.2 (q, *C*-8b), 78.6 (t, *C*-1), 55.8 (p, H_3CO-8), 54.8 (t, *C*-3), 54.7 (p, H_3CO-4'), 51.4 (p, H_3CO-11), 51.2 (t, *C*-2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{25}BrO_7Na$ $[M+Na]^+$ 563.0681 found 563.0665.

3-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (185)



185
$C_{17}H_{14}O_5$
MW: 298.29

Pyrrolidine (14.8 mL, 181 mmol, 10.0 eq.) was added to a suspension of finely grounded 1-(2-hydroxy-4-methoxy)ethenone (**184**) (3.00 g, 18.1 mmol, 1.00 eq.) and 4-methoxybenzaldehyde (2.42 mL, 19.9 mmol, 1.10 eq.) in a mixture of H_2O (120 mL) and MeOH (10.0 mL) at maximum stirring speed. The resulting mixture was stirred at 50 °C. Since the starting material was not completely converted after 24 h, a second portion of pyrroline (7.43 mL, 90.3 mmol, 5.00 eq.) and methanol (5.00 mL) was added. The mixture was stirred for another 16 h and then cooled to rt, subsequently poured into ice-cold H_2O and acidified to pH = 4 with HCl (37 wt%, aq.). The resulting precipitate was filtered and washed with H_2O. The crude product was recrystallized from aqueous ethanol (*v/v* 80%) to afford the desired flavonol **185** as a pale-yellow solid (1.35 g, 4.51 mmol) in 25% yield.

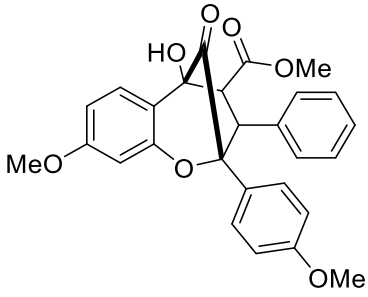
$\mathbf{R}_f$ = 0.48 (petroleum ether/EtOAc 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.18 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 8.09 (d, J = 8.9 Hz, 1H, Ar*H*), 7.01 (d, J = 8.9 Hz, 2H, 2x Ar*H*), 6.95 (dd, J = 8.9, 2.1 Hz, 1H, Ar*H*), 6.91 (d, J = 2.0 Hz, 1H, Ar*H*), 3.91 (s, 3H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.7 (q, *C*=O), 164.1 (q, Ar*C*), 160.9 (q, Ar*C*), 157.2 (q, Ar*C*), 144.7 (q, *C*=COH), 137.4 (q, *C*OH), 129.3 (t, 2x Ar*C*), 126.7 (t, Ar*C*H), 123.8 (q. Ar*C*), 114.8 (q, Ar*C*), 114.7 (t, Ar*C*H), 114.1 (t, 2x Ar*C*), 99.9 (s, O*C*H$_2$O), 55.9 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$).

The analytical data are consistent with those reported in the literature.[88]

(±)-Methyl (3*S*,4*S*,5*R*)-5-hydroxy-8-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E34)

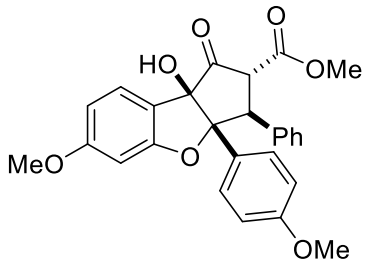


E34
$C_{27}H_{24}O_7$
MW: 460.48

Methyl cinnamate (3.86 g, 23.8 mmol, 14.2 eq.) was added to a solution of flavonol **185** (500 mg, 1.68 mmol, 1.00 eq.) in dry chloroform (32.9 mL) and freshly distilled 2,2,2-trifluoroethanol (14.0 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light

(λ_{max} = 365 nm) until it no longer fluoresced greenish (24 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 9:1 ⟶ 1:1). Product **E34** was obtained as a mixture of isomers as a yellowish glassy foam (685 mg) and used directly for the next step.

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-8b-hydroxy-6-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (E35)

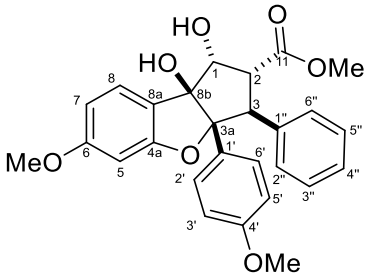


E35
$C_{27}H_{24}O_7$
MW: 460.48

Cycloadduct **E34** (685 mg, 1.49 mmol, 1.00 eq.) was dissolved in MeOH (55.1 mL). Then NaOMe solution (804 µL, 25 wt% in MeOH, 4.83 mmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E35** was obtained as a mixture of isomers as a brown foam (685 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.50 (petroleum ether/EtOAc 1:2).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-186)



(±)-186
$C_{27}H_{26}O_7$
MW: 462.50

A mixture of $(CH_3)_4N(OAc)_3BH$ (2.51 g, 9.55 mmol, 6.42 eq.) and freshly distilled AcOH (886 µL, 15.5 mmol, 10.4 eq.) in MeCN (38.6 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E35** (685 mg, 1.49 mmol, 1.00 eq.) in MeCN (25.7 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was

extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 10:1) was then performed to obtain the racemic *endo*-product **(±)-186** as a pale-yellow foam (270 mg, 584 µmol) in 35% yield over 3 steps.

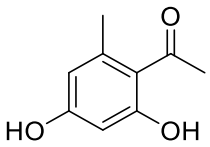
$\mathbf{R}_f$ = 0.49 (CH_2Cl_2/EtOAc 4:1).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.30 (d, $\mathcal{J}$ = 8.3 Hz, 1H, *H*-8), 7.07 – 6.99 (m, 5H, *H*-2', H-6', *H*-2'', *H*-4'', *H*-6''), 6.83 (d, $\mathcal{J}$ = 6.9 Hz, 2H, *H*-3'', *H*-5''), 6.66 – 6.62 (m, 3H, *H*-5, *H*-3', *H*-5'), 6.51 (dd, $\mathcal{J}$ = 8.4, 2.3 Hz, 1H, *H*-7), 5.72 (d, $\mathcal{J}$ = 5.8 Hz, 1H, O*H*-1), 5.28 (s, 1H, O*H*-8b), 4.76 (dd, $\mathcal{J}$ = 7.2, 6.0 Hz, 1H, *H*-1), 4.04 (d, $\mathcal{J}$ = 13.9 Hz, 1H, *H*-3), 3.87 (dd, $\mathcal{J}$ = 13.9, 7.4 Hz, 1H, *H*-2), 3.78 (s, 3H, H_3CO-8), 3.62 (s, 3H, H_3CO-4'), 3.51 (s, 3H, H_3CO-11).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 170.3 (q, *C*-11), 161.2 (q, *C*-6), 159.2 (q, *C*-4a), 157.7 (q, *C*-4'), 138.1 (q, *C*-1''), 128.7 (t, *C*-2', *C*-6'), 128.4 (t, *C*-8) 127.9 (q, *C*-1'), 127.7 (t, *C*-3'', *C*-5''), 127.5 (t, *C*-2'', *C*-6''), 126.1 (t, *C*-4''), 122.0 (q, *C*-8a), 112.1 (t, *C*-3', *C*-5'), 107.0 (t, *C*-7), 100.9 (q, *C*-3a), 95.8 (t, *C*-5), 91.4 (q, *C*-8b), 78.5 (t, *C*-1), 55.4 (p, H_3CO-6), 54.8 (p, H_3CO-4'), 54.1 (t, *C*-3), 51.3 (p, H_3CO-11), 50.2 (t, *C*-2).

The analytical data are consistent with those reported in the literature.[61]

1-(2,4-Dihydroxy-6-methylphenyl)ethan-1-one (188)



188
$C_9H_{10}O_3$
MW: 166.18

To a solution of orcinol (**187**) (3.21 g, 25.9 mmol, 1.00 eq.) and 3Å molecular sieve in freshly distilled AcOH (14.8 mL), $BF_3{\cdot}Et_2O$ (4.79 mL, 38.8 mmol, 1.50 eq.) was added dropwise over a period of 1 h at rt. After stirring at 90 °C for 18 h, the reaction mixture was terminated by addition of NH_4Cl solution (aq., sat.). The solvent was removed under reduced pressure, the residue was dissolved in EtOAc and washed with Na_2CO_3 solution (aq., sat.), H_2O and NaCl solution (aq., sat.). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product via silica gel column chromatography (EtOAc/petroleum ether = 1:6 ⟶ 1:3) gave the desired product **188** as a colorless solid (2.83 g, 17.0 mmol) in 66% yield.

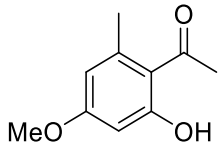
$\mathbf{R}_f$ = 0.62 (CH_2Cl_2/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.43 (bs, 1H, O*H*), 6.24 (dd, $\mathcal{J}$ = 7.8, 2.5 Hz, 2H, 2x Ar*H*), 2.62 (s, 3H, C(O)CH_3), 2.56 (s, 3H, ArCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.2 (q, *C*=O), 166.8 (q, Ar*C*), 160.8 (q, Ar*C*), 142.9 (q, Ar*C*), 115.6 (q, Ar*C*), 111.8 (t, Ar*C*H), 101.8 (q, Ar*C*), 33.1 (p, C(O)*C*H$_3$), 25.1 (p, Ar*C*H$_3$).

The analytical data are consistent with those reported in the literature.[234]

1-(2-Hydroxy-4-methoxy-6-methylphenyl)ethan-1-one (189)



189
$C_{10}H_{12}O_3$
MW: 180.20

To a solution of acetophenone **188** (2.83 g, 17.0 mmol, 1.00 eq.) in dry acetone (42.6 mL) were added anhydrous K_2CO_3 (2.35 g, 17.0 mmol, 1.00 eq.) and iodomethane (1.25 mL, 19.9 mmol, 1.17 eq.). The reaction mixture was heated under refluxing conditions for 1 h and then cooled to rt. The solvent was removed under reduced pressure. An oily solid remained to which H_2O was added. The resulting suspension was then filtered and the solid was first washed with H_2O and subsequently dissolved in CH_2Cl_2. The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then recrystallized from petroleum ether/CH_2Cl_2 (1:1) to give the desired product **189** as a colorless solid (948 mg, 5.26 mmol) in 31% yield.

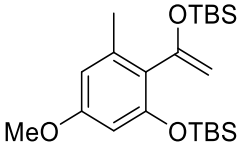
$\mathbf{R}_f$ = 0.74 (CH_2Cl_2/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.57 (bs, 1H, O*H*), 6.29 (dd, $\mathcal{J}$ = 10.2, 2.7 Hz, 2H, 2x Ar*H*), 3.80 (s, 3H, OCH_3), 2.62 (s, 3H, C(O)CH_3), 2.56 (s, 3H, ArCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.2 (q, *C*=O), 167.4 (q, Ar*C*), 164.6 (q, Ar*C*), 142.1 (q, Ar*C*), 115.4 (q, Ar*C*), 112.1 (t, Ar*C*H), 99.2 (t, Ar*C*H), 55.6 (p, O*C*H$_3$), 33.3 (p, C(O)*C*H$_3$), 25.4 (p, Ar*C*H$_3$).

The analytical data are consistent with those reported in the literature.[235]

tert-Butyl((1-(2-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-6-methylphenyl)vinyl)oxy) dimethylsilane (E36)

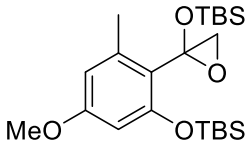


E36
$C_{22}H_{40}O_3Si_2$
MW: 408.73

A solution of acetophenone **189** (700 mg, 3.88 mmol, 1.00 eq.) in CH_2Cl_2 (7.80 mL) was cooled to 0 °C, treated with triethylamine (1.35 mL, 9.71 mmol, 2.50 eq.) and TBSOTf (2.05 mL, 8.93 mmol, 2.30 eq.) and stirred at 0 °C for 3 h. The reaction was terminated by the addition $NaHCO_3$ solution (aq., sat.) and was allowed to warm to rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yielding two-phasic mixture of the product and triethylammonium triflate was diluted with Et_2O and NH_4Cl solution (aq., sat.) and the phases were separated. The aqueous phase was extracted with Et_2O (3x). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Product **E36** was obtained as a yellowish oil (1.59 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.66 (petroleum ether/EtOAc 3:1).

tert-Butyl((2-(2-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-6-methylphenyl)oxiran-2-yl)oxy)dimethylsilane (E37)

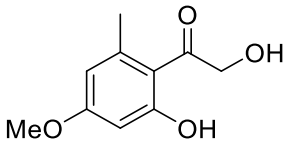


E37
$C_{22}H_{40}O_4Si_2$
MW: 424.73

The TBS enol ether **E36** (1.59 g, 3.88 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (3.75 mL) and added to a suspension of *m*CPBA (70 wt%, 1.34 g, 5.43 mmol, 1.40 eq.) and $NaHCO_3$ (701 mg, 8.34 mmol, 2.15 eq.) in CH_2Cl_2 (15.0 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred for 4 h. Then, the reaction mixture was diluted with CH_2Cl_2 (20.0 mL), washed with $NaHCO_3$ (aq., sat.) and H_2O, dried over $MgSO_4$ and filtered. After concentration under reduced pressure, product **E37** was obtained as a yellowish oil (1.59 g) and was used directly for the next step.

$\mathbf{R}_f$ = 0.70 (petroleum ether/EtOAc 3:1).

2-Hydroxy-1-(2-hydroxy-4-methoxy-6-methylphenyl)ethan-1-one (190)



190
$C_{10}H_{12}O_4$
MW: 196.20

A solution of crude epoxide **E37** (1.59 g, 3.74 mmol, 1.00 eq.) in THF (19.3 mL) and H_2O (1.93 mL) was treated with *p*TsOH·H_2O (71.1 g, 374 µmol, 10 mol%). The orange reaction mixture was heated under refluxing conditions for 20 h. The mixture was allowed to cool to rt and partitioned between EtOAc and $NaHCO_3$ solution (aq., sat.). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. After purification by column chromatography (petroleum ether/EtOAc 4.33:1 ⟶ 2:1) the desired product **190** was obtained as a pale-brown solid (130 mg, 663 µmol) in 17% yield over three steps.

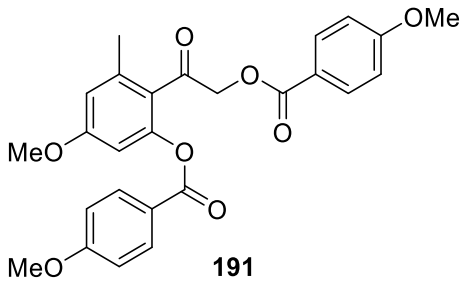
$\mathbf{R}_f$ = 0.54 (petroleum ether/EtOAc 3:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 13.14 (s, 1H, O*H*), 6.35 (d, $\mathcal{J}$ = 2.6 Hz, 1H, Ar*H*), 6.30 (dd, $\mathcal{J}$ = 2.3, 0.7 Hz, 1H, Ar*H*), 5.08 (s, 2H, CH_2), 4.72 (s, 2H, CH_2OH), 3.83 (s, 3H, OCH_3), 2.48 (s, 3H, ArCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 202.7 (q, *C*=O), 167.9 (q, Ar*C*), 165.5 (q, Ar*C*), 142.0 (q, Ar*C*), 112.6 (t, Ar*C*H), 110.8 (q, Ar*C*), 99.4 (t, Ar*C*H), 68.4 (s, *C*H_2OH), 55.7 (p, O*C*H_3), 24.6 (p, Ar*C*H_3).

HRMS (ESI$^+$) *m/z* calcd. for $C_{10}H_{12}O_4Na$ $[M+Na]^+$ 219.0633, found 219.0627.

2-(4-Methoxy-2-((4-methoxybenzoyl)oxy)-6-methylphenyl)-2-oxoethyl 4-methoxybenzoate (191)

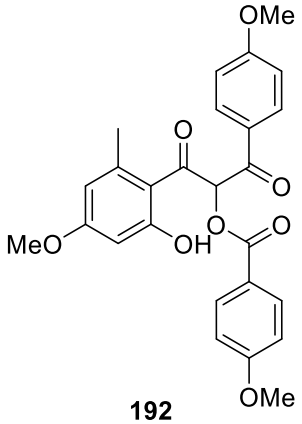


191
$C_{26}H_{24}O_8$
MW: 464.47

A solution of the α-hydroxy ketone **190** (130 mg, 663 µmol, 1.00 eq.) in CH_2Cl_2 (1.73 mL) was treated with 4-DMAP (4.05 mg, 33.1 µmol, 5 mol%) and triethylamine (276 µL, 1.99 mmol, 3.00 eq.). The mixture was cooled to 0 °C and 4-methoxybenzoyl chloride (179 µL, 1.33 mmol, 2.00 eq.) was added and stirred at rt for 3 h. The solution was terminated by the addition of HCl (1.00 M in H_2O) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired bisbenzoate **191** was purified by flash chromatography (petroleum ether/EtOAc 4:1) obtained as a yellow foam (228 mg) and was used directly for the next step.

$\mathbf{R}_f$ = 0.54 (petroleum ether/EtOAc 1:1).

1-(2-Hydroxy-4-methoxy-6-methylphenyl)-3-(4-methoxyphenyl)-1,3-dioxopropan-2-yl 4-methoxybenzoate (192)

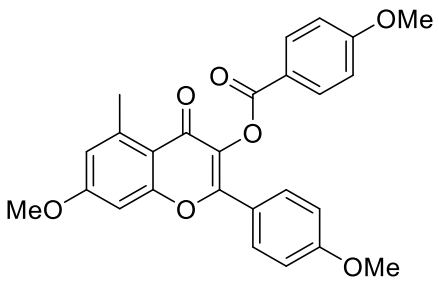


192
$C_{26}H_{24}O_8$
MW: 464.47

A solution of crude bisbenzoate **191** (228 mg, 491 µmol, 1.00 eq.) in THF (14.4 mL) was cooled to –20 °C and treated with LiHMDS (1.00 M in THF, 1.51 mL, 1.51 mmol, 3.00 eq.). The mixture was stirred at –20 °C for 2 h. Then, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.) and warmed to rt. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The desired phenol **192** was obtained as a yellow foam (212 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.20 (petroleum ether/EtOAc 1:1).

7-Methoxy-2-(4-methoxyphenyl)-5-methyl-4-oxo-4*H*-chromen-3-yl 4-methoxybenzoate (193)



193
$C_{26}H_{22}O_7$
MW: 446.46

A suspension of crude phenol **192** (212 mg, 456 µmol, 1.00 eq.) in AcOH (6.00 mL) was treated with H_2SO_4 (96 wt%, 120 µL, 2.17 mmol, 5.00 eq.) and stirred at rt for 20 h. The reaction mixture was poured into ice-cold H_2O and stirred for 15 min. Thereby, a pale-orange precipitate was formed. The mixture was filtered on a BÜCHNER funnel and the precipitate was washed with H_2O. The wet solid was suspended in a minimal amount of EtOH and heated to reflux for 1 h. The mixture was allowed to cool to rt, filtered on a BÜCHNER funnel and washed with a small amount of cold EtOH. The solid was dried under reduced pressure to constant weight to give the desired 3-benzyloxyflavonate **193** as yellowish solid (122 mg, 273 µmol) in 41% yield over three steps.

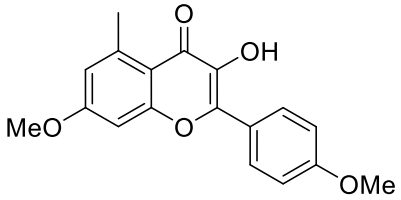
$\mathbf{R}_f$ = 0.43 (petroleum ether/EtOAc 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.18 (d, J = 8.7 Hz, 2H, 2x Ar*H*), 7.88 (d, J = 8.8 Hz, 2H, 2x Ar*H*), 6.96(t, J = 9.4 Hz, 4H, 4x Ar*H*), 6.81 (d, J = 1.9 Hz, 1H, Ar*H*), 6.72 (d, J = 1.7 Hz, 1H, Ar*H*), 5.16 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.84 (s, 3H, ArCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 173.4 (q, *C*=O), 164.2 (q, Ar*C*), 163.9 (q, Ar*C*), 162.9 (q, O*C*=O), 161.7 (q, Ar*C*), 159.0 (q, Ar*C*), 154.1 (q, *C*=C-C=O), 143.2 (q, Ar*C*), 133.8 (q, O=C-*C*=C), 132.9 (t, 2x Ar*C*), 129.9 (t, 2x Ar*C*), 122.6 (q, Ar*C*), 121.3 (q, Ar*C*), 116.5 (t, Ar*C*H), 116.2 (q, Ar*C*), 114.2 (t, 2x Ar*C*), 114.0 (t, 2x Ar*C*), 98.5 (t, Ar*C*H), 55.8 (p, O*C*H$_3$), 55.7 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$), 22.9 (p, Ar*C*H$_3$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{26}H_{22}O_7Na$ $[M+Na]^+$ 469.1263, found 469.1261.

3-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-5-methyl-4*H*-chromen-4-one (194)



194
$C_{18}H_{16}O_5$
MW: 312.32

A suspension of the benzoate **193** (122 mg, 263 µmol, 1.00 eq.) in EtOH (1.31 mL) was treated with NaOH solution (1.00 M in H_2O, 394 µL, 394 µmol, 1.50 eq.). The yellowish suspension was stirred at 80 °C for 4 h. The reaction mixture was allowed to cool to rt and was neutralized with HCl (1.00 M in

H_2O, 394 µL, 394 µmol, 1.50 eq.). The resulting suspension was filtered on a BÜCHNER funnel and the filter precipitate was washed with a small amount of cold EtOH. The residue was dried under reduced pressure to constant weight to give the desired 3-hydroxyflavone **194** as a yellowish solid (60.2 mg, 193 µmol) in 73% yield.

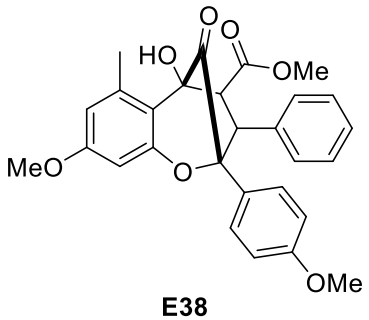
$\mathbf{R}_f$ = 0.60 (petroleum ether/EtOAc 1:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.18 (d, J = 8.6 Hz, 2H, 2x Ar*H*), 7.22 (bs, 1H, O*H*), 7.03 (d, J = 8.5 Hz, 2H, 2x Ar*H*), 6.79 (s, 1H, Ar*H*), 6.71 (s, 1H, Ar*H*), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.87 (s, 3H, ArCH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 174.1 (q, *C*=O), 162.9 (q, Ar*C*), 160.8 (q, Ar*C*), 158.7 (q, Ar*C*), 142.9 (q, *C*=COH), 142.1 (q, Ar*C*), 137.6 (q, *C*OH), 129.1 (t, 2x Ar*C*), 123.8 (q, Ar*C*), 116.3 (t, Ar*C*H), 114.1 (t, 2x Ar*C*), 113.3 (q, Ar*C*), 98.1 (t, Ar*C*H), 55.7 (p, O*C*H$_3$), 55.5 (p, O*C*H$_3$), 22.6 (p, Ar*C*H$_3$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{18}H_{16}O_5Na$ $[M+Na]^+$ 335.0895, found 335.0904.

(±)-Methyl (3*S*,4*S*,5*R*)-5-hydroxy-8-methoxy-2-(4-methoxyphenyl)-6-methyl-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (E38)

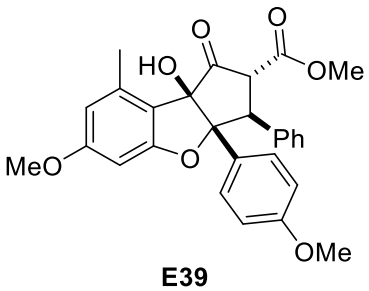


E38
$C_{28}H_{26}O_7$
MW: 474.51

Methyl cinnamate (442 mg, 2.73 mmol, 14.2 eq.) was added to a solution of flavonol **194** (60.2 mg, 193 µmol, 1.00 eq.) in dry chloroform (3.78 mL) and freshly distilled 2,2,2-trifluoroethanol (1.61 mL). The reaction mixture was degassed for 30 min, then cooled to −5 °C and irradiated with UV light (λ_{max} = 365 nm) until it no longer fluoresced greenish (20 h). Subsequently, the solvent was removed under reduced pressure. The remaining amount of methyl cinnamate was then removed by column chromatography (petroleum ether/EtOAc 4:1 → 1:1). Product **E38** was obtained as a mixture of isomers as a colorless foam (81.4 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.23 – 0.68 (petroleum ether/EtOAc 1:1).

(±)-Methyl (2*R*,3*S*,3a*R*,8b*R*)-8b-hydroxy-6-methoxy-3a-(4-methoxyphenyl)-8-methyl-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*] benzofuran-2-carboxylate (E39)

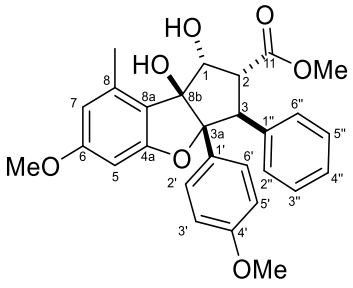


E39
$C_{28}H_{26}O_7$
MW: 474.51

Cycloadduct **E38** (81.4 mg, 172 µmol, 1.00 eq.) was dissolved in MeOH (6.35 mL). Then NaOMe solution (92.7 µL, 25 wt% in MeOH, 558 µmol, 3.25 eq.) was added and the mixture was heated under refluxing conditions for 1 h. Subsequently, the reaction was terminated by the addition of NH_4Cl solution (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Product **E39** was obtained as a mixture of isomers as a brownish, glassy foam (66.7 mg) and used directly for the next step.

$\mathbf{R}_f$ = 0.54 (petroleum ether/EtOAc 1:1).

(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-8-methyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-195)



(±)-195
$C_{28}H_{28}O_7$
MW: 476.53

A mixture of $(CH_3)_4N(OAc)_3BH$ (237 mg, 902 µmol, 6.42 eq.) and freshly distilled AcOH (84 µL, 1.46 mmol, 10.4 eq.) in MeCN (3.65 mL) was stirred for 5 min at rt. Then, a solution of keto ester **E39** (685 mg, 1.49 mmol, 1.00 eq.) in MeCN (2.42 mL) was added. The mixture was protected from light and stirred for 19 h at rt. The reaction was then terminated by adding NH_4Cl solution (aq., sat.) and sodium potassium tartrate solution (aq., 2.00 M). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (petroleum ether/EtOAc 3:1) was then performed to obtain the racemic *endo*-product **(±)-195** as a pale-yellow foam (26.9 mg, 56.5 µmol) in 29% yield over 3 steps.

$\mathbf{R}_f$ = 0.60 (petroleum ether/EtOAc 1:1).

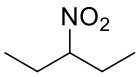
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.09 – 7.01 (m, 7H, *H*-2', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 6.60 (d, $\mathcal{J}$ = 8.9 Hz, 2H, *H*-3', *H*-5'), 6.45 (d, $\mathcal{J}$ = 1.8 Hz, 1H, *H*-5), 6.36 (d, $\mathcal{J}$ = 1.7 Hz, 1H, *H*-7), 4.78 (d, $\mathcal{J}$ = 4.4 Hz, 1H, *H*-1), 4.63 (d, $\mathcal{J}$ = 14.2 Hz, 1H, *H*-3), 4.03 (dd, $\mathcal{J}$ = 14.1, 4.5 Hz, 1H, *H*-2), 3.81 (s, 3H, H_3CO-6), 3.73 (s, 3H, CH_3O-11), 3.65 (s, 3H, H_3CO-4'), 2.36 (s, 3H, H_3C-8).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 172.1 (q, *C*-11), 162.8 (q, *C*-6), 161.4 (q, *C*-4a), 158.8 (q, *C*-4'), 138.3 (q, *C*-8), 137.3 (q, *C*-1''), 128.9 (t, *C*-2', *C*-6'), 128.1 (t, *C*-3'', *C*-5''), 128.0 (t, *C*-2'', *C*-6''), 127.0 (q, *C*-1'), 126.5 (t, *C*-4''), 115.9 (q, *C*-8a), 113.0 (t, *C*-3', *C*-5'), 109.8 (t, *C*-7), 101.8 (q, *C*-3a), 94.4 (q, *C*-8b), 93.8 (t, *C*-5), 78.4 (t, *C*-1), 56.1 (t, *C*-3), 55.6 (p, H_3CO-6), 55.2 (p, H_3CO-4'), 52.4 (p, H_3CO-11), 51.5 (t, *C*-2), 18.1 (p, H_3C-8).

HRMS (ESI$^+$) *m/z* calcd. for $C_{28}H_{28}O_7Na$ $[M+Na]^+$ 499.1733, found 499.1732.

E3 Experimental Procedures – Topic B

3-Nitropentane (299)



299
$C_5H_{11}NO_2$
MW: 117.15

$NaNO_2$ (18.3 g, 265 mmol, 1.60 eq.) was added to a solution of 3-bromopentane (**298**) (25.0 g, 166 mmol, 1.00 eq.) in DMSO (166 mL). The reaction mixture was stirred for 18 h at rt, cooled to 0 °C and H_2O was added until the formed precipitate was dissolved. The mixture was extracted with pentane (3 x 50.0 mL). The combined extracts were washed with H_2O (2 x 15.0 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Product **299** was obtained as a pale blue liquid (11.92 g, 102 mmol) in 61% yield and used without further purification.

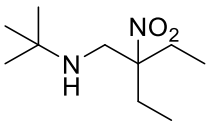
$\mathbf{R}_f$ = 0.73 (petroleum ether/EtOAc = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 4.32 (tt, $\mathcal{J}$ = 9.3, 4.6 Hz, 1H, C*H*NO_2), 1.97 (ddq, $\mathcal{J}$ = 14.6, 9.2, 7.3 Hz, 2H, 2x C*H*H), 1.78 (dqd, $\mathcal{J}$ = 14.8, 7.5, 4.6 Hz, 2H, 2x CH*H*), 0.95 (t, $\mathcal{J}$ = 7.4 Hz, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 91.9 (t, *C*HNO_2), 26.8 (s, 2x *C*H_2), 10.3 (p, 2x *C*H_3).

The analytical data are consistent with those reported in the literature.[200]

N-(*tert*-Butyl)-2-ethyl-2-nitrobutan-1-amine (300)



300
$C_{10}H_{22}N_2O_2$
MW: 202.30

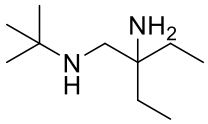
Formaldehyde (37 wt%, aq., 8.58 mL, 115 mmol, 1.00 eq.) was added slowly to *tert*-butylamine (12.1 mL, 115 mmol, 1.00 eq.) at 0 °C. Then, 3-nitropentane (**299**) (13.5 g, 115 mmol, 1.00 eq.) was added and the reaction mixture was stirred at rt. After 18 h, Na_2SO_4 was added until phase separation occurred. The aqueous layer was removed and the organic layer was stirred for additional 4 days at rt. The mixture was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Amine **300** was obtained after distillation as a colorless liquid (17.1 g, 8.45 mmol) in 73% yield.
bp = 88 °C (7 mbar).
$\mathbf{R}_f$ = 0.56 (petroleum ether/EtOAc = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 2.93 (s, 2H, CH_2NH), 1.97 (q, $\mathcal{J}$ = 7.5 Hz, 4H, 2x CH_2CH_3), 1.05 (s, 9H, 3x CH_3), 0.85 (t, $\mathcal{J}$ = 7.5 Hz, 6H, 2x CH_2CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 96.1 (q, *C*NO_2), 50.3 (q, *C*$(CH_3)_3$NH), 45.8 (s, *C*H_2NH), 29.2 (p, 3x *C*H_3), 26.3 (s, 2x *C*H_2CH_3), 8.1 (p, 2x CH_2*C*H_3).

The analytical data are consistent with those reported in the literature.[200]

*N*¹-(*tert*-Butyl)-2-ethylbutane-1,2-diamine (301)



301
$C_{10}H_{24}N_2$
MW: 172.32

A solution of amine **300** (17.0 g, 84.0 mmol, 1.00 eq.) in a mixture of AcOH (185 mL) and H_2O (120 mL) was cooled to 0 °C. Zinc powder (33.0 g, 504 mmol, 6.00 eq.) was added and the reaction mixture was stirred at rt for 2 h. The excess of zinc was filtered off and solid NaOH was added to the filtrate until the solution turned basic. The mixture was extracted with Et_2O (3 x 250 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain product **301** as a colorless liquid (14.5 g, 8.41 mmol) in 85% yield.

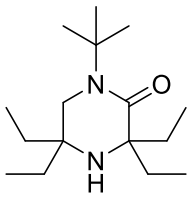
$\mathbf{R}_f$ = 0.30 (petroleum ether/EtOAc = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 2.34 (s, 2H, C*H*$_2$NH), 1.40 – 1.26 (m, 5H, 2x C*H*$_2$CH$_3$, N*H*), 1.09 (s, 1H, NH*H*), 1.05 (s, 10H, 3x C*H*$_3$, N*H*H), 0.81 (t, J = 7.5 Hz, 6H, 2x CH$_2$C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 53.5 (q, *C*NH$_2$), 50.0 (q, *C*(CH$_3$)$_3$NH), 49.7 (s, *C*H$_2$NH), 30.0 (s, 2x *C*H$_2$CH$_3$), 29.3 (p, 3x *C*H$_3$), 8.0 (p, 2x CH$_2$*C*H$_3$).

The analytical data are consistent with those reported in the literature.[200]

1-(*tert*-Butyl)-3,3,5,5-tetraethylpiperazin-2-one (302)



302
$C_{16}H_{32}N_2O$
MW: 268.45

Powdered KOH (3.45 mmol, 61.5 mmol, 3.00 eq.) was added slowly at 10 °C to a mixture of diamine **301** (2.00 g, 11.6 mmol, 1.00 eq.), 3-pentanone (18.9 mL, 174 mmol, 15.0 eq.) and $CHCl_3$ (1.49 ml, 18.6 mmol, 1.60 eq.). After stirring for for 18 h at rt, the reaction mixture filtered. The filtrate was evaporated to dryness and the crude product was purified by column chromatography (pentane/MTBE 10:1). Piperazinone **302** was obtained as a pale-yellow oil (953 mg, 3.55 mmol) in 31% yield.

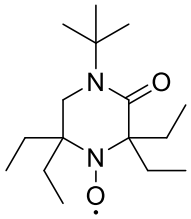
$\mathbf{R}_f$ = 0.21 (petroleum ether/Et_2O = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 3.15 (s, 2H, C*H*$_2$N), 1.58 (q, J = 7.5 Hz, 4H, 2x C*H*$_2$CH$_3$), 1.42 (s, 9H, 3x C*H*$_3$), 1.41-1.36 (m, 4H, 2x C*H*$_2$CH$_3$), 0.85 (q, J = 8.4 Hz, 12H, 4x C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 174.7 (q, *C*=O), 62.1 (q, *C*(C$_2$H$_5$)$_2$NH), 57.2 (q, *C*(CH$_3$)$_3$N), 53.6 (q, *C*(CH$_2$)$_3$N), 51.2 (s, *C*H$_2$N), 32.5 (s, 2x *C*H$_2$CH$_3$), 29.0 (p, 2x CH$_2$*C*H$_3$), 28.5 (p, 3x CH$_3$), 8.3 (p, 2x CH$_2$*C*H$_3$), 7.9 (p, 2x CH$_2$*C*H$_3$).

The analytical data are consistent with those reported in the literature.[200]

1-*tert*-Butyl-3,3′-diethyl-5,5′-dimethyl-2-piperazinon-4-oxyl (303f)



303f
$C_{16}H_{31}N_2O_2^{\bullet}$
MW: 283.44

Piperazinone **303** (300 mg, 1.12 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (5.00 mL). Then, *m*CPBA (501 mg, 2.24 mmol, 2.00 eq.) was added in small portions at 0 °C and the reaction mixture was allowed to warm to rt. After 16 h, a Na_2CO_3 solution (aq., 5 wt%, 10.0 mL) was added. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x 5.00 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The aminoxyl radical **303f** was collected after purification by flash column chromatography (petroleum ether/EtOAc 50:1 ⟶ 5:1) as an orange oil (279 mg, 984 µmol) in 88% yield.

$\mathbf{R}_f$ = 0.30 (petroleum ether/EtOAc = 10:1).

IR ν_{max} [cm^{-1}] 2967, 2940, 2882, 1653 ν(C=O), 1485, 1458, 1412, 1381, 1362, 1346, 1331, 1312, 1271, 1248, 1204, 1179, 1146, 1123.

HRMS (ESI$^+$) *m/z* calcd. for $C_{16}H_{32}N_2O_2$ $[M+H]^+$ 284.2464, found 284.2464.

The analytical data are consistent with those reported in the literature.[200]

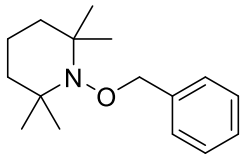
General Procedure A: Decarboxylative aminoxylation using water as solvent

A suspension of the of the carboxylic acid (200 µmol, 1.00 eq.), TEMPO (62.5 mg, 400 µmol, 2.00 eq.), K_2CO_3 (41.5 mg, 300 µmol, 1.50 eq.) and $K_2S_2O_8$ (162 mg, 600 µmol, 3.00 eq.) in H_2O (2.00 mL) was allowed to stir 20 h at rt. Then, the reaction mixture was diluted with a solution of ascorbic acid (10 wt%, aq., 3.00 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic phases were washed with $NaHCO_3$ solution (aq., sat., 10.0 mL) and NaCl solution (aq., sat., 10.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure.

General Procedure B: Decarboxylative aminoxylation using a biphasic solvent system

A vial charged with the carboxylic acid (200 µmol, 1.00 eq.), the aminoxyl radical (400 µmol, 2.00 eq.), K_2CO_3 (41 mg, 300 µmol, 1.50 eq.) and $K_2S_2O_8$ (54 mg, 200 µmol, 1.00 eq.) was evacuated and purged with argon. Then, DCE (1.50 mL) and H_2O (0.50 mL) were added. The biphasic mixture was allowed to stir 20 h at 80 °C under an argon atmosphere. Subsequently, the reaction mixture was diluted water (5.00 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic phases were washed with a solution of NaCl (aq., sat., 10.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure.

1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (293a)



293a
$C_{16}H_{25}NO$
MW: 247.38

This compound was prepared according to general procedure A using phenylacetic acid (**226a**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293a** was collected as a pale-yellow oil (45 mg, 182 µmol) in 91% yield.

This compound was also prepared according to general procedure B. In this case, alkoxyamine **293a** (41 mg, 166 µmol) was afforded in 83% yield.

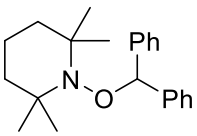
$\mathbf{R}_f$ = 0.50 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.38 – 7.28 (m, 5H, Ar*H*), 4.83 (s, 2H, CH_2ON), 1.64 – 1.34 (m, 6H, 3x CH_2), 1.26 (s, 6H, 2x CH_3), 1.16 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 138.5 (q, Ar*C*), 128.4 (t, 2x Ar*C*), 127.6 (t, 2x Ar*C*), 127.4 (t, Ar*C*), 78.9 (s, *C*H_2ON), 60.2 (q, 2x *C*(CH_3)$_2$), 39.9 (s, 2x *C*H_2), 33.2 (p, 2x *C*H_3), 20.4 (p, 2x *C*H_3), 17.3 (s, *C*H_2(CH_2)$_2$).

The analytical data are consistent with those reported in the literature.[236]

1-(Benzhydryloxy)-2,2,6,6-tetramethylpiperidine (293b)



293b
$C_{22}H_{29}NO$
MW: 323.48

This compound was prepared according to general procedure B using diphenylacetic acid (**294b**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293b** was collected as a colorless solid (38 mg, 117 µmol) in 59% yield.

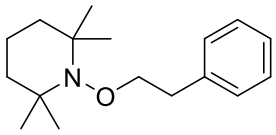
$\mathbf{R}_f$ = 0.34 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.41 (d, J = 7.4 Hz, 4H, Ar*H*), 7.30 (t, J = 7.6 Hz, 4H, Ar*H*), 7.19 (t, J = 7.2 Hz, 2H, Ar*H*), 5.64 (s, 1H, C*H*ON), 1.43-1.26 (m, 6H, 3x CH_2), 1.16 (s, 6H, 2x CH_3), 0.74 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 144.6 (q, 2x Ar*C*), 127.9 (t, 4x Ar*C*), 126.5 (t, 4x Ar*C*), 126.3 (t, 2x Ar*C*), 90.5 (t, *C*ON), 59.6 (q, 2x *C*(CH_3)$_2$), 40.2 (s, 2x *C*H_2), 33.7 (p, 2x *C*H_3), 20.2 (p, 2x *C*H_3), 16.9 (s, *C*H_2(CH_2)$_2$).

The analytical data are consistent with those reported in the literature.[237]

2,2,6,6-Tetramethyl-1-phenethoxypiperidine (293c)



293c
$C_{17}H_{27}NO$
MW: 261.41

This compound was prepared according to general procedure B using 3-phenylpropanoic acid (**294c**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293c** was collected as a pale-yellow oil (33 mg, 126 µmol) in 63% yield.

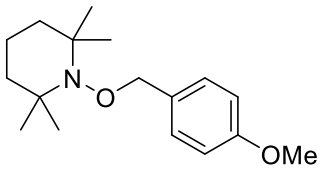
$\mathbf{R}_f$ = 0.41 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.30 – 7.17 (m, 5H, 5x Ar*H*), 3.95 (t, $\mathcal{J}$ = 7.0 Hz, 2H, CH_2ON), 2.83 (t, $\mathcal{J}$ = 7.0 Hz, 2H, CH_2CH_2ON), 1.56 – 1.23 (m, 6H, 3x CH_2), 1.07 (s, 12H, 4x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 139.8 (q, Ar*C*), 129.2 (t, 2x Ar*C*), 128.2 (t, 2x Ar*C*), 126.0 (t, Ar*C*), 77.6 (s, *C*H_2ON), 59.8 (q, 2x *C*$(CH_3)_2$), 39.7 (s, 2x *C*H_2), 35.5 (s, Ph*C*H_2), 33.1 (p, 2x *C*H_3), 20.3 (p, 2x *C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[238]

1-((4-Methoxybenzyl)oxy)-2,2,6,6-tetramethylpiperidine (293d)



293d
$C_{17}H_{27}NO_2$
MW: 277.41

This compound was prepared according to general procedure B using 4-methoxyphenylacetic acid (**294d**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293d** was collected as a pale-yellow oil (30 mg, 108 µmol) in 54% yield.

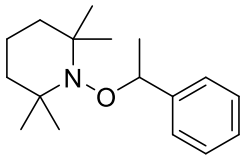
$\mathbf{R}_f$ = 0.31 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.30 (d, $\mathcal{J}$ = 8.6 Hz, 2H, 2x Ar*H*), 6.88 (d, $\mathcal{J}$ = 8.6 Hz, 2H, 2x Ar*H*), 4.74 (s, 2H, CH_2ON), 6.88 (s, 3H, OCH_3), 1.62 – 1.33 (m, 6H, 3x CH_2), 1.27 (s, 6H, 2x CH_3), 1.14 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 159.1 (q, Ar*C*), 130.5 (q, Ar*C*), 129.3 (t, 2x Ar*C*), 113.8 (t, 2x Ar*C*), 78.6 **(**s, *C*H_2ON), 60.1 **(**q, 2x*C*$(CH_3)_2$), 55.4 (p, O*C*H_3), 39.9 (s, 2x*C*H_2), 33.3 (p, 2x*C*H_3), 20.4 (p, 2x*C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$**).**

The analytical data are consistent with those reported in the literature.[239]

2,2,6,6-Tetramethyl-1-(1-phenylethoxy)piperidine (293e)



293e
$C_{17}H_{27}NO$
MW: 261.41

This compound was prepared according to general procedure B using 2-phenylpropanoic acid (**294e**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293e** was collected as a colorless oil (32 mg, 122 µmol) in 61% yield.

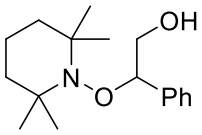
$\mathbf{R}_f$ = 0.39 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.43 – 7.29 (m, 4H, 4x Ar*H*), 7.25 – 7.21 (m, 1H, Ar*H*), 4.79 (q, $\mathcal{J}$ = 6.7 Hz, C*H*ON), 1.62 – 1.34 (m, 6H, 3x CH_2), 1,49 (d, $\mathcal{J}$ = 6.7 Hz, CH_3CHON), 1.30 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.67 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 146.0 (q, Ar*C*), 128.1 (t, 2x Ar*C*), 126.9 (t, Ar*C*), 126.7 (t, 2x Ar*C*), 83.3 (t, *C*HON), 59.8 (q, 2x *C*$(CH_3)_2$), 40.5 (s, 2x *C*H_2), 34.6 (p, *C*H_3), 34.3 (p, *C*H_3), 23.7 (p, *C*H_3), 20.5 (p, 2x *C*H_3), 17.4 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[192]

2-Phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethan-1-ol (293f)



293f
$C_{17}H_{27}NO_2$
MW: 277.41

This compound was prepared according to general procedure B using tropic acid (**294f**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 15:1 ⟶ 5:1). Alkoxyamine **293f** was collected as a pale-yellow oil (32 mg, 115 µmol) in 58% yield.

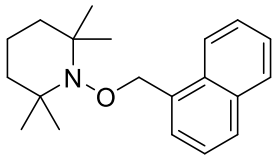
$\mathbf{R}_f$ = 0.32 (petroleum ether/EtOAc 10:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.38 – 7.28 (m, 5H, 5x Ar*H*), 5.86 (bs, 1H, O*H*), 5.31 (dd, $\mathcal{J}$ = 9.5, 2.4 Hz, 1H, C*H*ON), 4.23 (dd, $\mathcal{J}$ = 12.2, 9.5 Hz, 1H, C*H*HOH), 3.73 (dd, $\mathcal{J}$ = 12.2, 2.6 Hz, 1H, CH*H*OH), 1.66 – 1.38 (m, 6H, 3x CH_2), 1.52 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.16 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 138.9 (q, Ar*C*), 128.3 (t, 2x Ar*C*), 127.9 (t, Ar*C*), 126.8 (t, 2x Ar*C*), 83.6 (t, *C*HON), 69.7 (s, *C*H_2OH), 61.7 (q, *C*$(CH_3)_2$), 60.4 (q, *C*$(CH_3)_2$), 40.4 (s, *C*H_2), 40.2 (s, *C*H_2), 34.6 (p, *C*H_3), 32.8 (p, *C*H_3), 20.7 (p, *C*H_3), 20.4 (p, *C*H_3), 17.2 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[240]

2,2,6,6-Tetramethyl-1-(naphthalen-1-ylmethoxy)piperidine (293g)



293g
$C_{20}H_{27}NO$
MW: 297.44

This compound was prepared according to general procedure A using naphthaleneacetic acid (**294g**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293g** was collected as a colorless oil (44 mg, 148 µmol) in 72% yield.

This compound was also prepared according to general procedure B. In this case, alkoxyamine **293g** (45 mg, 151 µmol) was afforded in 76% yield.

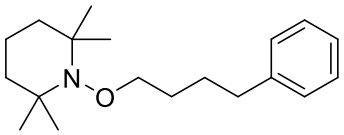
$\mathbf{R}_f$ = 0.36 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.05 (d, J = 8.1 Hz, 1H, Ar*H*), 7.88 (d, J = 8.1 Hz, 1H, Ar*H*), 7.80 (d, J = 8.3 Hz, 1H, Ar*H*), 7.65 (d, J = 7.0 Hz, 1H, Ar*H*), 7.56 – 7.47 (m, 3H, 3x Ar*H*), 5.33 (s, 2H, CH_2ON), 1.66 – 1.38 (m, 6H, 3x CH_2), 1.34 (s, 6H, 2x CH_3); 1.21 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 134.6 (q, Ar*C*), 133.6 (q, Ar*C*), 131.4 (q, Ar*C*), 128.6 (t, Ar*C*), 127.7 (t, Ar*C*), 126.0 (t, Ar*C*), 125.6 (t, Ar*C*), 125.6 (t, Ar*C*), 125.0 (t, Ar*C*), 124.0 (t, Ar*C*), 77.0 (s, *C*H_2ON), 60.2 (q, 2x *C*$(CH_3)_2$), 39.9 (s, 2x *C*H_2), 33.3 (p, 2x *C*H_3), 20.5 (p, 2x *C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[241]

2,2,6,6-Tetramethyl-1-(4-phenylbutoxy)piperidine (293j)



293j
$C_{19}H_{31}NO$
MW: 289.46

This compound was prepared according to general procedure B using 5-phenylvaleric acid (**294j**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293j** was collected as a colorless oil (11 mg, 38 µmol) in 19% yield.

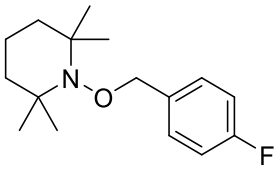
$\mathbf{R}_f$ = 0.27 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.28 (t, J = 6.5 Hz, 2H, 2x Ar*H*), 7.18 (t, J = 8.1 Hz, 3H, 3xAr*H*), 3.76 (t, J = 6.5 Hz, 2H, CH_2ON), 2.64 (t, J = 7.7 Hz, 2H, PhCH_2), 1.71 (qi, J = 7.6 Hz, 2H, PhCH$_2$CH_2), 1.60 – 1.53 (m, 2H, CH_2CH$_2$ON), 1.46 – 1.23 (m, 6H, 3x CH_2), 1.15 (s, 6H, 2x CH_3), 1.09 (s, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 142.8 (q, Ar*C*), 128.6 (t, 2x Ar*C*), 128.4 (t, 2x Ar*C*), 125.8 (t, Ar*C*), 76.7 (s, *C*H2ON), 59.8 (q, 2x*C*$(CH_3)_2$), 39.7 (s, 2x*C*H_2), 36.1 (s, Ph*C*H_2), 33.2 (p, 2x*C*H_3), 28.6 (s, PhCH$_2$*C*H$_2$), 28.5 (s, *C*H_2CH$_2$ON), 20.3 (p, 2x *C*H_3), 17.3 (s, *C*$H_2(CH_2)$).

HRMS (ESI$^+$) *m/z* calcd. for $C_{19}H_{31}NO$ $[M+H]^+$ 290.2484, found 290.2484.

1-((4-Fluorobenzyl)oxy)-2,2,6,6-tetramethylpiperidine (293k)



293k
$C_{16}H_{24}FNO$
MW: 265.37

This compound was prepared according to general procedure B using 4-fluorophenylacetic acid (**294k**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293k** was collected as a pale-yellow oil (41 mg, 155 µmol) in 77% yield.

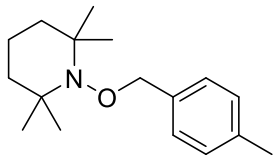
$\mathbf{R}_f$ = 0.37 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.32 (dd, J = 8.4, 5.6 Hz, 2H, 2x Ar*H*), 7.02 (t, J = 8.7 Hz, 2H, 2x Ar*H*), 4.78 (s, 2H, CH_2ON), 1.62 – 1.34 (m, 6H, 3x CH_2), 1.25 (s, 6H, 2x CH_3), 1.14 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 162.3 (doublet, q, Ar*C*F), 134.1 (doublet, q, Ar*C*), 129.3 (doublet, t, 2x Ar*C*), 115.2 (doublet, t, 2x Ar*C*), 78.2 (doublet, s, *C*H_2ON), 60.1 (q, 2x *C*$(CH_3)_2$), 39.8 (s, 2x *C*H_2), 33.2 (p, 2x *C*H_3), 20.4 (p, 2x *C*H_3), 17.2 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[242]

2,2,6,6-Tetramethyl-1-((4-methylbenzyl)oxy)piperidine (293l)



293l
$C_{17}H_{27}NO$
MW: 261.41

This compound was prepared according to general procedure B using 4-methylphenylacetic acid (**294l**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293l** was collected as a colorless oil (37 mg, 142 µmol) in 71% yield.

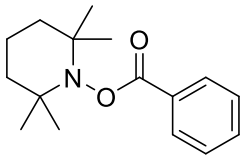
$\mathbf{R}_f$ = 0.38 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.27 (d, J = 7.9 Hz, 2H, 2x Ar*H*), 7.16 (d, J = 7.9 Hz, 2H, 2x Ar*H*), 4.79 (s, 2H, CH_2ON), 2.36 (s, 3H, PhCH_3), 1.64 – 1.35 (m, 6H, 3x CH_2), 1.28 (s, 6H, 2x CH_3), 1.16 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 137.1 (q, Ar*C*), 135.4 (q, Ar*C*), 129.1 (t, 2x Ar*C*), 127.8 (t, 2x Ar*C*), 78.8 (s *C*H_2ON), 60.1 (q, 2x *C*$(CH_3)_2$), 39.9 (s, 2x *C*H_2), 33.3 (p, 2x *C*H_3), 21.3 (p, Ph*C*H_3), 20.4 (p, 2x *C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[242]

2,2,6,6-Tetramethylpiperidin-1-yl benzoate (293m)



293m
$C_{16}H_{23}NO_2$
MW: 261.37

This compound was prepared according to general procedure B using phenylglyoxylic acid (**294m**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/Et_2O 6:1). Ester **293m** was collected as a colorless solid (20 mg, 77 µmol) in 38% yield.

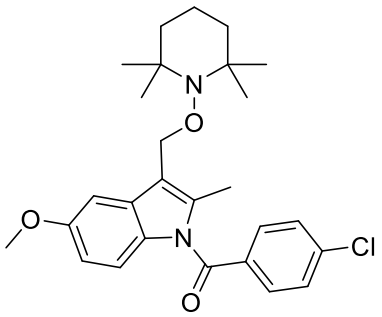
$\mathbf{R}_f$ = 0.62 (petroleum ether/Et_2O 6:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.07 (dd, J = 8.4, 1.2 Hz, 2H, 2x Ar*H*), 7.56 (tt, J = 7.4, 1.3 Hz, 1H, Ar*H*), 7.46 (t, J = 7.6 Hz, 2H, 2x Ar*H*), 1.81 – 1.43 (m, 6H, 3x CH_2), 1.27 (s, 6H, 2x CH_3), 1.12 s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 166.5 (q, *C*=O), 133.0 (t, Ar*C*), 129.9 (q, Ar*C*), 129.7 (t, 2x Ar*C*), 128.6 (t, 2x Ar*C*), 60.5 (q, 2x *C*(CH_3)$_2$), 39.2 (s, 2x *C*H_2), 32.1 (p, 2x *C*H_3), 21.0 (p, 2x *C*H_3), 17.1 (s, *C*H_2(CH_2)$_2$).

The analytical data are consistent with those reported in the literature.[243]

(4-Chlorophenyl)(5-methoxy-2-methyl-3-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-1*H*-indol-1-yl)methanone (293n)



293n
$C_{27}H_{33}ClN_2O_3$
MW: 469.02

This compound was prepared according to general procedure B using indomethacin (**294n**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 10:1). Alkoxyamine **293n** was afforded as a yellow oil (28 mg, 60 µmol) in 31% yield.

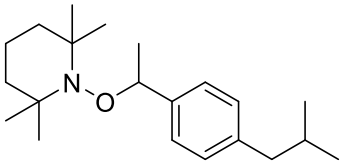
$\mathbf{R}_f$ = 0.43 (petroleum ether/EtOAc 10:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] ; 7.76 (d, J = 8.0 Hz, 2H, 2x Ar*H*), 7.55 (d, J = 8.0 Hz, 2H, 2x Ar*H*), 7.22 (d, J = 1.6 Hz, 1H, Ar*H*), 6.92 (d, J = 8.9 Hz, 1H, Ar*H*), 6.74 (dd, J = 8.9, 1.6 Hz, 1H, Ar*H*), 4.99 (s, 2H, CH_2ON), 3.91 (s, 3H, OCH_3), 2.51 (s, 3H, ArCH_3), 1.70 – 1.46 (m, 6H, 3x CH_2), 1.44 (s, 6H, 2x CH_3), 1.20 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 168.6 (q, *C*=ON), 156.0 (q, Ar*C*OCH_3), 139.4 (q, Ar*C*Cl), 136.5 (q, Ar*C*CH_3), 134.1 (q, Ar*C*C=O), 131.4 (t, 2x Ar*C*), 131.04 (q, Ar*C*), 131.03 (q, Ar*C*), 129.3 (t, 2x Ar*C*), 116.8 (q, Ar*C*CH_2ON), 114.9 (t, Ar*C*), 111.6 (t, Ar*C*), 102.2 (t, Ar*C*), 69.9 (s, *C*H_2ON), 60.0 (q, 2x*C*$(CH_3)_2$), 55.8 (p, O*C*H_3), 39.9 (s, 2x *C*H_2), 33.6 (p, 2x *C*H_3), 20.3 (p, 2x *C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$), 13.7 (p, *C*H_3CNC=O).

HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{33}N_2O_3NaCl$ $[M+Na]^+$ 491.2077, found 491.2073.

1-(1-(4-Isobutylphenyl)ethoxy)-2,2,6,6-tetramethylpiperidine (293o)



293o
$C_{21}H_{35}NO$
MWt: 317.52

This compound was prepared according to general procedure B using ibuprofen (**294o**) and TEMPO (**221**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **293o** was afforded as a pale-yellow oil (38 mg, 120 µmol) in 60% yield.

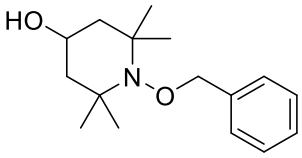
$\mathbf{R}_f$ = 0.36 (petroleum ether/EtOAc 50:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.22 (d, $\mathcal{J}$ = 7.9 Hz, 2H, 2x Ar*H*), 7.08 (d, $\mathcal{J}$ = 7.9 Hz, 2H, 2x Ar*H*), 4.75 (q, $\mathcal{J}$ = 6.6 Hz, 1H, C*H*ON), 2.46 (d, $\mathcal{J}$ = 7.2 Hz, 2H, PhCH_2), 1.86 (h, $\mathcal{J}$ = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.54 – 1.27 (m, 6H, 3x CH_2), 1.48 (d, $\mathcal{J}$ = 6.7 Hz, 3H, CH_3CHON), 1.29 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.89 (d, $\mathcal{J}$ = 6.6 Hz, 6H, 2x $(CH_3)_2$CH), 0.63 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 143.1 (q, Ar*C*CH_2), 140.3 (q, Ar*C*CH), 128.8 (t, 2x Ar*C*), 126.6 (t, 2x Ar*C*), 82.9 (t, *C*HON), 59.8 (q, 2x*C*$(CH_3)_2$), 45.3 (s, Ar*C*H_2), 40.5 (s, 2x *C*H_2), 34.5 (p, *C*H_3), 34.2 (p, *C*H_3), 30.4 (p, *C*H_3CHON), 29.8 (t, *C*H$(CH_3)_2$), 23.4 (p, C*C*H_3), 22.50 (p, *C*H_3CH), 22.49 (p, *C*H_3CHCH_2), 20.5 (p, C*C*H_3), 17.4 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[244]

1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-ol (304a)



304a
$C_{16}H_{25}NO_2$
MW 263.38

This compound was prepared according to general procedure B using phenylacetic acid (**226a**) and 4-OH-TEMPO (**303a**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 2:1 ⟶ 1:1). Alkoxyamine **304a** was collected as a pale-yellow oil (39 mg, 148 µmol) in 74% yield.

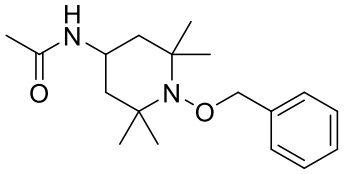
$\mathbf{R}_f$ = 0.44 (petroleum ether/EtOAc 3:2).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.41 – 7.38 (m, 4H, 4x Ar*H*), 7.35 – 7.32 (m, 1H, Ar*H*), 4.88 (s, 2H, CH_2ON), 4.07 (t, J = 11.0 Hz, 1H, C*H*OH), 1.90 (d, J = 10.6 Hz, CH_2, 2H), 1.58 (t, J = 11.4 Hz, 2H, CH_2), 1.35 (s, 6H, 2x CH_3), 1.26 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 137.3 (q, Ar*C*), 127.6 (t, 2x Ar*C*), 126.8 (t, 2x Ar*C*), 126.7 (t, Ar*C*), 78.2 (s, *C*H_2ON), 62.5 (t, *C*HOH). 59.6 (q, 2x *C*$(CH_3)_2$), 47.7 (s, 2x CH_2), 32.5 (p, 2x *C*H_3), 20.5 (p, 2x *C*H_3).

The analytical data are consistent with those reported in the literature.[181]

N-(1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-yl)acetamide (304b)



304b
$C_{18}H_{28}N_2O_2$
MW: 304,.43

This compound was prepared according to general procedure B using phenylacetic acid (**226a**) and 4-acetamido-TEMPO (**303b**). The product was then purified using flash column chromatography (CH_2Cl_2/MeOH 95:5). Alkoxyamine **304b** was collected as a colorless solid (50 mg, 164 µmol) in 82% yield.

R$_f$ = 0.41 (CH_2Cl_2/MeOH 95:5).

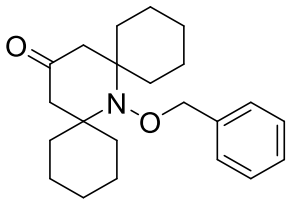
mp = 126 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.35 – 7.33 (m, 4H, 4x Ar*H*), 7.30 – 7.27 (m, 1H, Ar*H*), 5.44 (bs, 1H, N*H*), 4.82 (s, 2H, CH_2ON), 4.17 (t, J = 13.3 Hz, 1H, C*H*NH), 1.96 (s, 3H, CH_3C=O), 1.82 (dd, J = 12.3, 3.1 Hz, 2H, CH_2), 1.38 (t, J = 12.0 Hz, 2H, CH_2), 1.28 (s, 6H, 2x CH_3), 1.26 (s, 6H, 2x CH_3).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ [ppm] 169.2 (q, *C*=O), 137.3 (q, Ar*C*), 128.2 (t, 2x Ar*C*), 127.3 (t, 3x Ar*C*), 78.7 (s, *C*H_2ON), 60.1 (q, 2x *C*$(CH_3)_2$). 45.7 (s, 2x CH_2), 40.9 (t, *C*HNH), 32.9 (p, 2x *C*H_3), 23.5 (s, CH_3), 20.7 (p, 2x *C*H_3).

HRMS (ESI$^+$) *m/z* calcd. for $C_{18}H_{29}N_2O_2$ $[M+H]^+$ 305.2229, found 305.2228.

7-(Benzyloxy)-7-azadispiro[5.1.5^8.3^6]hexadecan-15-one (304c)



304c
$C_{22}H_{31}NO_2$
MW: 341.49

This compound was prepared according to general procedure B using phenylacetic acid (**226a**) and (15-oxo-7-azadispiro[5.1.5.3]hexadec-7-yl)oxidanyl (**303c**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 9:1). Alkoxyamine **304c** was collected as a colorless oil (40 mg, 117 µmol) in 58% yield.

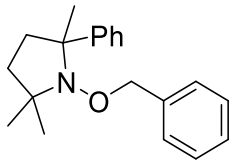
$\mathbf{R}_f$ = 0.35 (petroleum ether/EtOAc 9:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.38 – 7.28 (m, 5H, 5x Ar*H*), 4.92 (s, 2H, CH_2ON), 2.78 (d, J = 13.3 Hz, 2H, 2x C*H*HC=O), 2.38 (d, J = 13.4 Hz, 2H, 2x CH*H*C=O), 2.03 (td, J = 19.5, 4.3 Hz, 2H, CH_2), 1.97 (td, J = 12.6, 3.7 Hz, 2H, CH_2), 1.80 – 1.56 (m, 10H, 5x CH_2), 1.43 – 1.26 (m, 4H, 2x CH_2), 1.18 – 1.07 (m, 2H, CH_2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 209.4 (q, *C*=O), 137.6 (q, Ar*C*), 128.5 (t, 2x Ar*C*), 127.7 (q, Ar*C*), 127.4 (t, 2x Ar*C*), 79.5 (s, *C*H_2ON), 67.6 (q, 2x *C*Cy), 47.2 (s, 2x *C*H_2C=O), 39.2 (s, 2x *C*H_2), 32.5 (s, 2x *C*H_2), 25.6 (s, 2x *C*H_2), 23.1 (s, 2x *C*H_2), 22.8 (s, 2x *C*H_2).

HRMS (ESI$^+$) *m/z* calcd. for $C_{22}H_{31}NO_2$ $[M+H]^+$ 342.2433, found 342.2436.

1-(Benzyloxy)-2,2,5-trimethyl-5-phenylpyrrolidine (304d)



304d
$C_{20}H_{25}NO$
MW: 295.43

This compound was prepared according to general procedure B using phenylacetic acid (**226a**) and 2,5,5-trimethyl-2-phenylpyrrolidin-1-yloxyl (**303d**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1). Alkoxyamine **304d** was afforded as a colorless oil (35 mg, 122 µmol) in 61% yield.

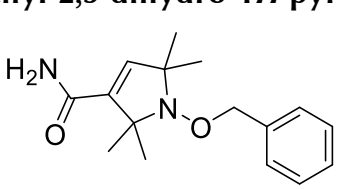
$\mathbf{R}_f$ = 0.45 (petroleum ether/EtOAc 20:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.37 (d, J = 7.4 Hz, 2H, 2x Ar*H*), 7.37 – 7.22 (m, 8H, 8x Ar*H*), 4.65 (d, J = 10.8 Hz, 1H, C*H*HON), 4.51 (d, J = 10.8 Hz, 1H, CH*H*ON), 2.06 – 1.92 (m, 2H, CH_2), 1.77 – 1.67 (m, 2H, CH_2), 1.65 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.29 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 151.2 (q, Ar*C*), 138.3 (q, Ar*C*), 128.4 (t, 2x Ar*C*), 128.2 (t, 2x Ar*C*), 127.9 (t, 2x Ar*C*), 127.6 (q, Ar*C*), 126.3 (t, 2x Ar*C*), 126.0 (t, Ar*C*), 77.6 (s, *C*H_2ON), 68.5 (q, *C*(CH_3)Ph), 64.6 (q, *C*(CH_3)$_2$), 39.3 (s, *C*H_2), 36.0 (s, *C*H_2), 30.4 (p, *C*H_3), 23.5 (p, 2x *C*H_3).

HRMS (ESI$^+$) *m/z* calcd. for $C_{20}H_{26}NO$ $[M+H]^+$ 296.2014, found 296.2013.

1-(Benzyloxy)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide (304e)



304e
$C_{16}H_{22}N_2O_2$
MW: 274.36

This compound was prepared according to general procedure B using phenylacetic acid (**226a**) and 3-carbamoyl-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**303e**). The product was then purified using

flash column chromatography (petroleum ether/EtOAc 3:2). Alkoxyamine **304e** was collected as a colorless solid (17 mg, 62 µmol) in 31% yield.

$\mathbf{R}_f$ = 0.29 (petroleum ether/EtOAc 3:2).

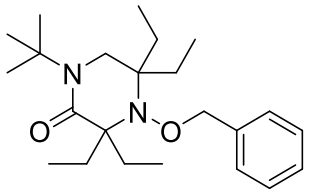
mp = 123 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.40 – 7.28 (m, 5H, 5x Ar*H*), 6.05 (s, 1H, C*H*=$CONH_2$), 5.59 (bs, 2H, N*H*$_2$), 4.85 (s, 2H, C*H*$_2$ON), 1.45 (s, 6H, 2x C*H*$_3$), 1.27 (s, 6H, 2x C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 166.8 (q, *C*ONH_2), 139.7 (q, *C*$CONH_2$), 139.5 (t, *C*H=C$CONH_2$), 138.2 (q, Ar*C*), 128.6 (t, 2x Ar*C*), 128.4 (t, 2x Ar*C*), 127.9 (t, Ar*C*), 79.5 (*C*H_2ON), 70.9 (q, *C*$(CH_3)_2$), 68.0 (q, *C*$(CH_3)_2$), 29.8 (p, 2x *C*H_3), 23.1 (p, 2x *C*H_3).

HRMS (ESI$^+$) *m/z* calcd. for $C_{16}H_{23}N_2O_2$ $[M+H]^+$ 275.1760, found 275.1775.

4-(Benzyloxy)-1-(*tert*-butyl)-3,3,5,5-tetraethylpiperazin-2-one (304f)



304f
$C_{23}H_{38}N_2O_2$
MW: 374.57

This compound was prepared according to general procedure B using phenylacetic acid (**226a**) and 4-*tert*-butyl-2,2,6,6-tetraethyl-3-oxo-piperazin-1-oxyl (**303f**). The product was then purified using flash column chromatography (petroleum ether/MTBE 10:1). Alkoxyamine **304f** was collected as a colorless viscous oil (22 mg, 59 µmol) in 29% yield.

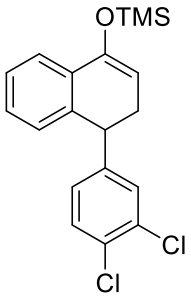
$\mathbf{R}_f$ = 0.33 (petroleum ether/MTBE 10:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.36 – 7.26 (m, 5H, 5x Ar*C*), 4.76 (q, J = 12.4 Hz, 2H, C*H*$_2$ON), 3.23 (d, J = 12.6 Hz, 1H, C*H*HN), 3.07 (d, J = 12.6 Hz, 1H, CH*H*N), 2.07 – 1.93 (m, 2H, C*H*$_2$$CH_3$), 1.89 – 1.70 (m, 4H, 2x C*H*$_2$$CH_3$), 1.63 – 1.56 (m, 2H, C*H*$_2$$CH_3$), 1.41 (s, 3xCC*H*$_3$), 1.00 (t, J = 7.4 Hz, 9H, 3x CH_2C*H*$_3$), 0.92 (t, J = 7.4 Hz, 3H, CH_2C*H*$_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 173.2 (q, *C*=ON), 137.6 (q, Ar*C*), 128.4 (t, Ar*C*), 127.9 (t, Ar*C*), 127.7 (q, Ar*C*), 77.9 (s, *C*H_2ON), 73.0 (q, CO*C*$(C_2H_5)_2$), 62.8 (q, CH_2*C*$(C_2H_5)_2$), 57.4 (q, *C*$(CH_3)_3$), 47.1 (s, *C*H_2N), 33.1 (s, *C*$H_2$$CH_3$), 29.0 (), 28.3 (p, 3x C(*C*H3)$_3$), 26.5 (s, *C*$H_2$$CH_3$), 24.2 (s, *C*$H_2$$CH_3$), 11.4 (p, CH_2*C*H_3), 9.4 (p, CH_2*C*H_3), 9.1 (p, CH_2*C*H_3), 8.2 (p, CH_2*C*H_3).

HRMS (ESI$^+$) *m/z* calcd. for $C_{23}H_{38}N_2O_2Na$ $[M+Na]^+$ 397.2831, found 397.2831.

((4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1-yl)oxy)trimethylsilane (310)



310
$C_{19}H_{20}Cl_2OSi$
MW: 363.35

To a solution of the tetralone **306** (1.00 g, 3.26 mmol, 1.00 eq.) in dry CH_2Cl_2 (5.00 mL) Et_3N (498 µL, 3.59 mmol, 1.10 eq.) and TMSOTf (591 µL, 13.26 mmol, 1.00 eq.) were added at 0 °C. The reaction was stirred at the same temperature for 30 min, and immediately subjected to flash column chromatography on silica that had been pre-treated with EtOAc and petroleum ether (1:10). The compound was eluted with petroleum ether. Silyl enol ether **310** was obtained as a colorless oil (1.13 g, 3.11 mmol) in 95% yield.

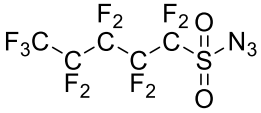
$\mathbf{R}_f$ = 0.20 (petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.51 (d, J = 7.7 Hz, 1H, Ar*H*), 7.31 (d, J = 8.3 Hz, 1H, Ar*H*), 7.24 (t, J = 8.4 Hz, 2H, 2x Ar*H*), 7.12 (td, J = 11.1, 1.1 Hz, 1H, Ar*H*), 7.00 (dd, J = 8.3, 1.9 Hz, 1H, Ar*H*), 6.81 (d, J = 7.5 Hz, 1H, Ar*H*), 5.07 (t, J = 4.6 Hz, 1H, C*H*=COTMS), 4.02 (t, J = 7.6 Hz, 1H, C*H*Ar), 2.70 (ddd, J = 16.5, 7.0, 4.5 Hz, 1H, C*H*H), 2.52 (ddd, J = 16.5, 8.2, 4.8 Hz, 1H, CH*H*), 0.24 (s, 9H, Si(C*H*$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 148.2 (q. *C*OTMS), 144.9 (q, Ar*C*), 138.0 (q, Ar*C*), 133.5 (q, Ar*C*), 132.4 (q, Ar*C*), 130.44 (q, Ar*C*), 130.38 (t, Ar*C*), 130.35 (t, Ar*C*), 128.1 (t, Ar*C*), 128.0 (t, Ar*C*), 127.6 (t, Ar*C*), 127.2 (t, Ar*C*), 122.6 (t, Ar*C*), 103.0 (t, *C*H=COTMS), 43.3 (t, *C*HAr), 30.7 (s, *C*H$_2$), 0.4 (p, 3x *C*H$_3$).

HRMS (EI) *m/z* calcd. for $C_{19}H_{20}Cl_2OSi$ $[M]^+$ 362.0660, found 362.0669.

1,1,2,2,3,3,4,4,5,5,5-Undecafluoropentane-1-sulfonyl azide (E40)



E40
$C_5F_{11}N_3O_2S$
MW: 375.12

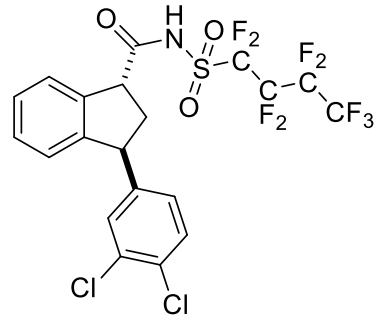
Perfluorobutanesulfonyl fluoride (2.00 g, 6.36 mmol, 1.00 eq.) was added to a solution of NaN_3 (413 mg, 6.63 mmol, 1.00 eq.) in dry MeOH (7.30 mL). The mixture was stirred for 18 h at rt. Then, it was passed over a fritted glass funnel to remove the solid precipitates. The filtrate was diluted with H_2O (10.0 mL). The fluorous phase was collected and dried over sodium sulfate to afford the neat nonaflyl azide (**E40**) as a colorless oil (1.06 g, 3.25 mmol) in 51% yield.

^{19}F NMR (376 MHz, $CDCl_3$): δ [ppm] −80.9 (tt, J = 14.5, 2.5 Hz, 3F, C*F*$_3$), −189.6 (tq, J = 20.5, 2.5 Hz, 2F, C*F*$_2$CF$_3$), −121.1 – −121.2 (m, 2F, SO$_2$CF$_2$C*F*$_2$), −126.0 – −126.2 (m, 2F, SO$_2$C*F*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 118.9 – 118.0 (m, 1C, CF_3), 166.0 – 115.0 (m, 1C, CF_2SO_2), 113.7 – 105.3 (m, 2C, 2x CF_2).

The analytical data are consistent with those reported in the literature.[245]

(±)-(1*R*,3*S*)-3-(3,4-Dichlorophenyl)-*N*-((perfluorobutyl)sulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide (311)



311

$C_{20}H_{12}Cl_2F_9NO_3S$

MW: 588.27

TMS-enol ether **310** (500 mg, 1.38 mmol, 1.00 eq.) was added to a solution of nonaflyl azide (**E40**) (492 mg, 1.51 mmol, 1.10 eq.) in MeCN (4.60 mL) at rt. After stirring the mixture for 20 h at 40 °C, the solvent was removed under reduced pressure. The residue obtained was purified by flash-column chromatography (CH_2Cl_2/EtOAc = 1:0 ⟶ 1:1). *N*-acyl sulfonamide **20** was obtained as an inseparable mixture of diastereomers (*anti:syn* 9:1) as a colorless solid (571 mg, 971 µmol) in 71% yield.

R$_f$ = 0.41 (CH_2Cl_2/EtOAc = 1:1).

mp = 96-99 °C.

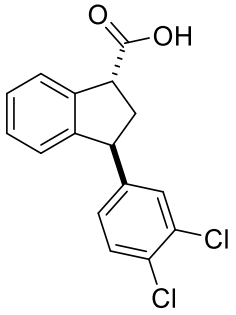
^{1}H NMR (400 MHz, DMSO): δ [ppm] 7.58 – 7.53 (m, 1H, Ar*H*), 7.47 – 7.38 (m, 2H, 2x Ar*H*), 7.24 – 7.11 (m, 3H, 3x Ar*H*), 6.87 (d, J = 7.1 Hz, 1H, Ar*H*, major), 6.77 (d, J = 7.1 Hz, 1H, Ar*H*, minor), 4.55 (t, J = 7.6 Hz, 1H, C*H*C=O, major), 4.33 (t, J = 8.9 Hz, 1H, C*H*C=O, minor), 3.96 (dd, J = 8.1, 3.9 Hz, 1H, C*H*($C_6H_3Cl_2$), major), 3.87 (t, J = 8.7 Hz, 1H, C*H*($C_6H_3Cl_2$), minor), 2.79 (ddd, J = 12.7, 8.5, 4.2 Hz, 1H, C*H*H, major), 2.66 – 2.58 (m, 1H, C*H*H, minor), 2.32 – 2.23 (m, 1H, CH*H*, minor), 2.09 (dt, J = 12.9, 7.7 Hz, 1H, CH*H*, major).

^{19}F NMR (376 MHz, MeOD): δ [ppm] −82.7 (tt, J = 10.0, 2.6 Hz, 3F, C*F*$_3$), −114.0 (t, J = 14.3 Hz, 2F, C*F*$_2$SO2), −122.4 – −122.6 (m, 2F, C*F*$_2$CF$_3$), −127.3 – −127.4 (m, 2F, C*F*$_2$CF$_2$SO$_2$).

^{13}C NMR (100 MHz, DMSO-*d*6): δ [ppm] 177.3 (q, CON), 146.9 (q, Ar*C*), 145.9 (q, Ar*C*), 143.7 (q, Ar*C*), 131.0 (q, Ar*C*), 130.7 (t, Ar*C*), 129.7 (t, Ar*C*), 128.8 (q, Ar*C*), 128.1 (t, Ar*C*), 127.1 (t, Ar*C*), 126.7 (t, Ar*C*), 125.0 (t, Ar*C*), 124.4 (t, Ar*C*), 118.5 – 110.5 (m, 4C, *C*F2*C*F2*C*F2*C*F3), 53.2 (t, *C*HC=O), 48.9 (t, *C*H($C_6H_3Cl_2$)), 38.8 (s, *C*H$_2$).

HRMS (ESI$^-$) *m/z* calcd. for $C_{20}H_{11}NO_3SCl_2F_9$ $[M–H]^-$ 585.9693, found 585.9695.

(±)-(1*R*,3*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid (312)



312
$C_{16}H_{12}Cl_2O_2$
MW: 307.17

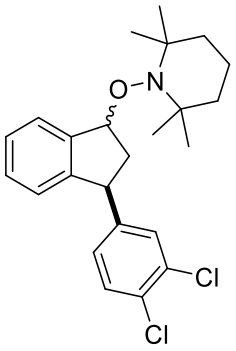
N-acyl sulfonamide **311** (552 mg, 938 µmol, 1.00 eq.) was dissolved in a mixture of 1,4-dioxane (9.40 mL) and H_2SO_4 (25 wt%, aq., 9.40 mL). The reaction mixture was heated under refluxing conditions for 20 h. Subsequently, water (5.00 mL) and CH_2Cl_2 (5.00 mL) were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x 5.00 mL). The combined organic layers were basified with NaOH (1.00 M, aq., 20.0 mL). The phases were separated and the organic phase was extracted with NaOH (1.00 M, aq., 2x 20.0 mL). The combined aqueous phases were washed with CH_2Cl_2 (20.0 mL) and then acidified to pH=1 using HCl (37 wt%, aq.). The colorless suspension was extracted with EtOAc (3x 50.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Residues of nonaflyl amine were removed by sublimation at 80 °C under high vacuum (~ 1 mbar). Carboxylic acid **312** was obtained a pale-yellow solid (251 mg, 817 µmol) in 87% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] 12.52 (bs, 1H, CO_2H), 7,59 (d, J = 8.3 Hz, 1H Ar*H*, minor), 7.56 (d, J = 8.3 Hz, 1H, Ar*H*, major), 7.47 – 7.42 (m, 2H, Ar*H*), 7.27 – 7.15 (m, 3H, Ar*H*), 6.91 (d, J = 7.3 Hz, 1H, Ar*H*, major), 6.86 (d, J = 7.2 Hz, 1H, Ar*H*, minor), 4.59 (t, J = 8.0 Hz, 1H, C*H*CO_2H, major), 4.41 (t, J = 8.7 Hz, 1H, C*H*CO_2H, minor), 4.17 (dd, J = 8.3, 3.3 Hz, 1H, *C*H($C_6H_3Cl_2$), major), 4.09 (t, J = 8.7 Hz, 1H, *C*H($C_6H_3Cl_2$), minor), 2.79 (ddd, J = 13.1, 8.4, 4.1 Hz, 1H, C*H*H), 2.24 (dt, J = 13.2, 8.1 Hz, 1H, CH*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ [ppm] 174.6 (q, *C*O_2H), 146.2 (q, Ar*C*), 145.9 (q, Ar*C*), 141.4 (q, Ar*C*), 131.1 (q, Ar*C*), 130.7 (t, Ar*C*), 129.9 (t, Ar*C*), 129.0 (q, Ar*C*), 128.2 (t, Ar*C*), 127.8 (t, Ar*C*), 127.2 (t, Ar*C*), 125.0 (t, Ar*C*), 124.7 (t, Ar*C*), 48.9 (t, *C*HC=O), 48.6 (t, *C*H($C_6H_3Cl_2$)), 38.2 (s, *C*H_2).

The analytical data are consistent with those reported in the literature.[246]

1-((3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (313)



313
$C_{24}H_{29}Cl_2NO$
MW: 418.40

A vial charged with carboxylic acid **312** (62 mg, 200 µmol, 1.00 eq.), TEMPO (**221**) (64 mg, 400 µmol, 2.00 eq.), K_2CO_3 (41 mg, 300 µmol, 1.50 eq.) and $K_2S_2O_8$ (54 mg, 200 µmol, 1.00 eq.) was evacuated and purged with argon. Then DCE (1.50 mL) and H_2O (500 µL) were added. The biphasic mixture was allowed to stir for 20 h at 80 °C under an argon atmosphere. Then, the reaction mixture was diluted water (5.00 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic phases were washed with a solution of NaCl (sat, aq., 10.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was then purified using flash column chromatography (petroleum ether/EtOAc 50:1 ⟶ 10:1). Alkoxyamine **313** was collected as an inseparable mixture of diastereomers (*anti*:*syn* 1:1.3) as a viscous red oil (43 mg, 103 µmol) in 51% yield.

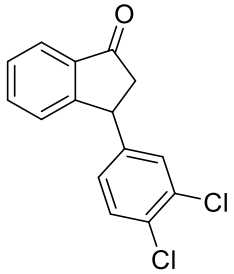
$\mathbf{R}_f$ = 0.41 (EtOAc/petroleum ether = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.68 (d, J = 7.4 Hz, 1H, Ar*H*, minor), 7.64 (t, J = 4.3 Hz, 1H, Ar*H*, major), 7.41 – 7.22 (m, 4H, 4x Ar*H*), 7.09 (d, J = 8.1 Hz, 1H, Ar*H*, minor), 6.99 (t, J = 3.9 Hz, 1H, Ar*H*, major), 6.94 (d, J = 8.1 Hz, 1H, Ar*H*, major), 6.89 (d, J = 7.3 Hz, 1H, Ar*H*, minor), 5.46 (t, J = 4.9 Hz, 1H, C*H*ON, major), 5.41 (t, J = 7.6 Hz, 1H, C*H*ON, minor), 4.48 (t, J = 6.9 Hz, 1H, C*H*($C_6H_3Cl_2$), major), 3.99 (dd, J = 10.1, 6.8 Hz, 1H, C*H*($C_6H_3Cl_2$), minor), 3.00 (dt, J = 12.3, 6.4 Hz, 1H, C*H*H, minor), 2.72 (ddd, J = 12.5, 7.7, 4.2 Hz, 1H, C*H*H, major), 2.28 (dt, J = 12.9, 6.3 Hz, 1H, CH*H*, major), 2.02 (q, J = 10.6 Hz, 1H, CH*H*, minor), 1.59 – 1.13 (m, 15H, 3x CH_2, 3x CH_3), 0.87 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]; 146.1 (q, Ar*C*, major), 145.5 (q, Ar*C*, major), 144.5 (q, Ar*C*, minor), 144.3 (q, Ar*C*, minor), 144.1 (q, Ar*C*, minor), 144.0 (q, Ar*C*, major), 132.6 (q, Ar*C*, minor), 132.5 (q, Ar*C*, major), 130.59 (q, Ar*C*, major), 130.58 (t, Ar*C*, minor), 130.53 (t, Ar*C*, minor), 130.49 (t, Ar*C*, major), 130.3 (q, Ar*C*, minor), 130.0 (t, Ar*C*, major), 128.8 (t, Ar*C*, major), 128.2 (t, Ar*C*, minor), 128.0 (t, Ar*C*, minor), 127.5 (t, Ar*C*, major), 127.1 (t, Ar*C*, minor), 126.8 (t, Ar*C*, major), 126.7 (t, Ar*C*, major),125.0 (t, Ar*C*, major), 124.7 (t, Ar*C*, minor), 124.5 (t, Ar*C*, minor), 87.3 (t, *C*HON, minor), 86.0 (*t*, *C*HON, major), 61.2 (q, *C*(CH_3)$_2$, major), 60.3 (q, *C*(CH_3)$_2$, minor), 59.9 (q, *C*(CH_3)$_2$, minor), 59.1 (q, *C*(CH_3)$_2$, major), 48.4 (t, *C*H($C_6H_3Cl_2$, major), 47.6 (s, *C*H_2, minor), 47.4 (t, *C*H($C_6H_3Cl_2$, minor), 44.7 (s, *C*H_2, major), 40.6 (s, 2x *C*H_2C(CH_3)$_2$, minor), 40.5 (s, 2x *C*H_2C(CH_3)$_2$, major), 34.91 (p, *C*H_3, minor), 34.86 (p, *C*H_3, major), 33.4 (p, *C*H_3, major), 33.2 (p, *C*H_3, minor), 20.6 (p, 2x *C*H_3, major), 20.5 (p, 2x *C*H_3, minor), 17.4 (s, *C*H_2(CH_2)$_2$, major), 17.3 (s, *C*H_2(CH_2)$_2$, minor).

HRMS (ESI$^+$) *m/z* calcd. for $C_{24}H_{29}Cl_2NO$ $[M+H]^+$ 418.1704, found 418.1708.

3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one (314)



314
$C_{15}H_{10}Cl_2O$
MW: 277.14

To a solution of the alkoxyamine **313** (80 mg, 191 µmol, 1.00 eq.) in CH_2Cl_2 (3.00 mL), *m*CPBA was added portionwise at 0 °C. The mixture was stirred at the same temperature for 90 min, then, $Na_2S_2O_3$ solution (aq., sat., 5.00 mL) was added to terminate the reaction and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3x 5.00 mL). The combined organic phases were washed with $NaHCO_3$ solution (aq., sat., 10.0 mL) and NaCl solution (aq., sat., 10.0 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (petroleum ether/EtOAc 15:1 ⟶ 5:1) and washed with ice-cold petroleum ether. Indenone **314** was collected as colorless solid (49 mg, 177 µmol) in 92% yield.

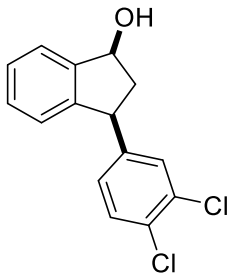
$\mathbf{R}_f$ = 0.26 (EtOAc/petroleum ether = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.83 (d. J = 7.6 Hz, 1H, Ar*H*), 7.61 (td. J = 7.5, 1.2 Hz, 1H, Ar*H*), 7.46 (t. J = 7.5 Hz, 1H, Ar*H*), 7.38 (d. J = 8.2 Hz, 1H, Ar*H*), 7.26 (d. J = 7.7 Hz, 1H, Ar*H*), 7.23 (d. J = 2.1 Hz, 1H, Ar*H*), 7.23 (dd. J = 8.2, 2.1 Hz, 1H, Ar*H*), 4.55 (dd. J = 8.1, 3.8 Hz, 1H, C*H*($C_6H_4Cl_2$)), 3.23 (dd. J = 19.2, 8.1 Hz, 1H, C*H*H), 2.62 (dd. J = 19.2, 3.9 Hz, 1H, CH*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 205.1 (q, *C*=O), 156.7 (q, Ar*C*), 144.1 (q, Ar*C*), 136.9 (q, Ar*C*), 135.5 (t, Ar*C*), 133.1 (q, Ar*C*), 131.2 (q, Ar*C*), 131.0 (t, Ar*C*), 129.8 (t, Ar*C*), 128.5 (t, Ar*C*), 127.1 (t, Ar*C*), 126.8 (t, Ar*C*), 123.8 (t, Ar*C*), 46.6 (s, *C*H_2), 43.7 (t, *C*H($C_6H_3Cl_2$)).

The analytical data are consistent with those reported in the literature.[247]

(±)-(1*S*,3*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (315)



315
$C_{15}H_{12}Cl_2O$
MW: 279.16

A solution of indenone **314** (21 mg, 76 µmol, 1.00 eq.) in anhydrous THF (230 µL) was cooled to –10 °C. Then, K-Selectride® (1.00 M in THF, 152 µL, 152 µmol, 2.00 eq.) was added dropwise and the reaction mixture was stirred for 4 h at the same temperature. Subsequently, H_2O (500 µL) was added slowly

and the solution was stirred for 30 min at rt. THF was removed under reduced pressure and the mixture was portioned between water (5.00 mL) and EtOAc (5.00 mL). The phases were separated and the aqueous was extracted with EtOAc (2 x 5.00 mL). The combined organic layers were washed with water (10.0 mL) and NaCl solution (aq., sat., 10.0 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (petroleum ether/EtOAc 10:1 ⟶ 3:1) to give *syn*-alcohol **315** (*dr* > 20:1) as a colorless solid (15 mg, 54 µmol) in 71% yield.

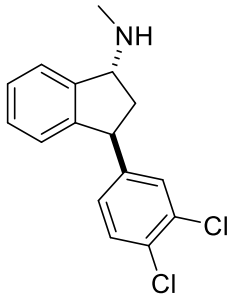
$\mathbf{R}_f$ = 0.42 (EtOAc/petroleum ether = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.48 (d, J = 7.4 Hz, 1H, Ar*H*), 7.39 – 7.23 (m, 4H, 4x Ar*H*), 7.07 (dd, J = 8.3, 2.0 Hz, 1H, Ar*H*), 6.93 (d, J = 7.3 Hz, 1H, Ar*H*), 5.30 (t, J = 7.1 Hz, 1H, C*H*OH), 4.16 (t, J = 8.2 Hz, 1H, C*H*($C_6H_3Cl_2$)), 3.02 (dt, J = 14.5, 6.6 Hz, 1H, C*H*H), 2.07 (bs, 1H, O*H*), 1.90 (ddd, J = 12.9, 8.8, 7.4 Hz, 1H, CH*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 145.3 (q, Ar*C*), 144.8 (q, Ar*C*), 144.6 (q, Ar*C*),132.7 (q, Ar*C*), 130.7 (t, Ar*C*), 130.4 (t, Ar*C*), 129.8 (q, Ar*C*), 128.8 (t, Ar*C*), 127.83 (t, Ar*C*), 127.80 (t, Ar*C*), 125.1 (t, Ar*C*), 124.1 (t, Ar*C*), 75.0 (t, *C*HOH), 47.7 (t, *C*H($C_6H_3Cl_2$)), 46.9 (s, *C*H_2).

The analytical data are consistent with those reported in the literature.[205]

(±)-(1*R*,3*S*)-3-(3,4-Dichlorophenyl)-*N*-methyl-2,3-dihydro-1*H*-inden-1-amine ((±)-Indatraline, 305)



305
$C_{16}H_{15}Cl_2N$
MW: 292.20

Et_3N (56 µL, 400 µmol, 4.00 eq.) was added to a solution of *syn*-alcohol **315** (28 mg, 100 µmol, 1.00 eq.) in anhydrous THF (850 µL). The mixture was cooled to −20 °C, MsCl (16 µL, 200 µmol, 2.00 eq.) was added dropwise, and the reaction mixture was stirred for 1 h at −20°C. Then, a solution of methylamine (1.00 mL, 2.00 M in THF, 2.00 mmol, 20.0 eq.) was added slowly. The mixture was allowed to warm to rt over 90 min and was then stirred for 20 h. Subsequently, the solvent was removed in vacuo. The residue was dissolved in water (10.0 mL) and EtOAc (10.0 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 x 10.0 mL). The combined organic layers were washed with NaCl solution (aq., sat., 2 x 20.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (silica was pretreated treated with Et_3N, petroleum ether/EtOAc 2:3 ⟶ 0:1) to give (±)-indatraline (**305**) as a yellow oil (23 mg, 82 µmol) in 82% yield.

$\mathbf{R}_f$ = 0.24 (CH_2Cl_2/MeOH = 15:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.40 (d, J = 6.8 Hz, 1H, Ar*H*), 7.35 (d, J = 8.2 Hz, 1H, Ar*H*), 7.29 – 7.22 (m, 3H, 3x Ar*H*), 6.97 (d, J = 8.0 Hz, 2H, 2x Ar*H*), 4.51 (t, J = 7.6 Hz, 1H, C*H*($C_6H_3Cl_2$)), 4.27 (dd, J = 6.6, 3.1 Hz, 1H, C*H*NHMe), 2.51 (s, 3H, CH_3N), 2.45 (ddd, J = 13.1, 7.9, 3.2 Hz, 1H, C*H*H), 2.24 (qi, J = 6.9 Hz, 1H, CH*H*).

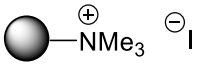
^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 145.7 (q, Ar*C*), 145.6 (q, Ar*C*), 145.0 (q, Ar*C*), 132.6 (q, Ar*C*), 130.6 (t, Ar*C*), 130.4 (q, Ar*C*), 130.0 (t, Ar*C*), 128.5 (t, Ar*C*), 127.6 (t, Ar*C*), 127.4 (t, Ar*C*), 125.4 (t, Ar*C*), 124.8 (t, Ar*C*), 63.8 (t, *C*HNHMe), 48.7 (t, *C*H($C_6H_3Cl_2$)), 43.4 (s, CH_2), 34.3 (p, *C*H_3NH).

HRMS (ESI$^+$) *m/z* calcd. for $C_{16}H_{16}NCl_2$ $[M+H]^+$ 292.0660, found 292.0669.

The analytical data are consistent with those reported in the literature.[206]

Synthesis of polymer-bound reagents[209]

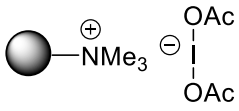
Polymer-bound iodide (264)



264

Polymer-bound hydroxide (Amberlyst® A26-resin; 4.2 mmol OH^-/g, 1.00 eq.) was flushed successively with NaOH (1.00 M, aq., 4.00 mL/g polymer), LiI solution (aq., sat., 5.00 mL/g polymer), H_2O (4.00 mL/g polymer), *i*PrOH (4.00 mL/g polymer) and CH_2Cl_2 (4 mL/g polymer). Drying under reduced pressure afforded a pale-pink resin **264**.

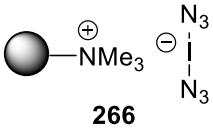
Polymer-bound bis(acetoxy)iodate(I) (265)



265

A suspension of polymer-bound iodide **265** (4.20 mmol I^-/g, 1.00 eq.) and $PhI(OAc)_2$ (1.80 eq.) in dry CH_2Cl_2 (3.00 mL/mmol iodide) was protected from light and was stirred for 6 h at rt under an argon atmosphere. The pale-yellow resin **265** was filtered, washed with CH_2Cl_2 (30.0 mL/g resin) and dried under reduced pressure.

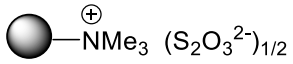
Polymer-bound bis(azido)iodate(I) (266)



266

A suspension of polymer-bound iodide **265** (4.20 mmol $I(OAc)_2^-$/g, 1.00 eq.) and $TMSN_3$ (2.60 equiv.) in dry CH_2Cl_2 (4.00 mL/mmol $I(OAc)_2^-$) was protected from light and was stirred for 6 h at rt under an argon atmosphere. The orange-colored resin **266** was filtered, washed with CH_2Cl_2 (30 mL/g resin) and dried under reduced pressure. Practically, the effective loading was found to be up to 2.1 mmol reagent per g resin.

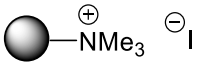
Polymer-bound thiosulfate (E41)



E41

Polymer-bound hydroxide (Amberlyst® A26-resin; 4.2 mmol OH^-/g, 1.00 eq.) was flushed successively with NaOH (1.00 M, aq., 4.00 mL/g polymer), $Na_2S_2O_3$ solution (aq., sat., 5.00 mL/g polymer), MeOH (4.00 mL/g polymer), acetone (4.00 mL/g polymer) and Et_2O (4.00 mL/g polymer). Drying *in vacuo* afforded the pale-pink resin **E41**.

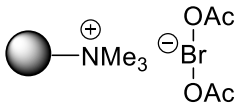
Polymer-bound bromide (264)



264

Polymer-bound hydroxide (Amberlyst® A26-resin; 4.2 mmol OH^-/g, 1.00 eq.) was flushed successively with NaOH (1.00 M, aq., 4.00 mL/g polymer), LiBr solution (aq., sat., 5.00 mL/g polymer), H_2O (4.00 mL/g polymer), *i*PrOH (4.00 mL/g polymer) and CH_2Cl_2 (4 mL/g polymer). Drying under reduced pressure afforded a pale-pink resin **350**.

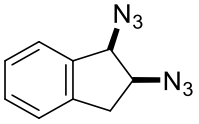
Polymer-bound bis(acetoxy)broate(I) (352)



352

A suspension of polymer-bound bromide **351** (3.50 mmol I^-/g, 1.00 eq.) and $PhI(OAc)_2$ (1.80 eq.) in dry CH_2Cl_2 (3.00 mL/mmol iodide) was protected from light and was stirred for 20 h at rt under an argon atmosphere. The yellow resin **265** was filtered, washed with CH_2Cl_2 (30.0 mL/g resin) and dried *in vacuo*.

(±)-(1*R*,2*S*)-1,2-Diazido-2,3-dihydro-1*H*-indene (274)



274
$C_9H_8N_6$
MW: 200.21

A mixture of the indene (**272**) (35 µL, 0.3 mmol, 1.00 eq.) and polymer **266** (573 mg, 1.21 mmol, 4.00 eq. based on the effective loading of 2.10 mmol/g resin) was stirred under blue LED light in absolute CH_2Cl_2 (1.70 mL) at rt under an argon atmosphere. After 20 h the reaction was terminated by filtration and the resin was washed with CH_2Cl_2. Polymer-bound thiosulfate was added and the reaction mixture was stirred for 10 min until the solution was nearly colorless. Then, the solution was filtered through a pad of cotton, filtered and concentrated under reduced pressure. Subsequently, the product was purified using flash column chromatography (hexanes/Et_2O 100:1 ⟶ 50:1). Bisazide **274** (*syn/trans* 8:1) was collected as a colorless oil (14 mg, 69 µmol) in 23% yield.

$\mathbf{R}_f$ = 0.21 (petroleum ether/Et_2O 40:1).

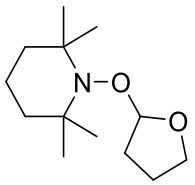
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.47 – 7.27 (m, 4H, 4x Ar*H*), 4.84 (d, J = 5.6 Hz, 1H, PhC*H*N_3), 4.29 (td, J = 6.6, 5.6 Hz, 1H, PhCHN_3C*H*N_3), 3.25 – 3.10 (m, 2H, PhC*H*$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 139.9 (q, Ar*C*), 137.7 (q, Ar*C*), 129.9 (t, Ar*C*H), 127.9 (t, Ar*C*H), 125.5 (t, Ar*C*H), 125.1 (t, Ar*C*H), 67.1 (t, Ar*C*HN_3), 64.2 (t, ArCH_2*C*HN_3), 35.7 (s, *C*H_2).

IR ν_{max} [cm^{-1}] 2099 ν(N_3).

The analytical data are in accordance with those reported in the literature.[248]

2,2,6,6-Tetramethyl-1-((tetrahydrofuran-2-yl)oxy)piperidine (324)



324
$C_{13}H_{25}NO_2$
MW: 227.25

TEMPO (**221**) (48.0 mg, 0.30 mmol, 1.00 eq.) was dissolved in freshly distilled dry THF (1.50 mL). Polymer **266** (571 mg, 1.00 mmol, 4.00 eq. based on the effective loading of 2.10 mmol/g resin) was added subsequently. The reaction mixture was stirred for 24 h under blue LED light irradiation. Then the polymer was filtered off to stop the reaction and polymer-bound thiosulfate (**E41**) was added to reduce the iodine formed. After stirring for another 10 minutes, the polymer was removed by filtration and the filtrate was concentrated under reduced pressure. The product was then purified using flash column chromatography (petroleum ether/Et_2O = 10:1). The desired product **324** was afforded as a colorless oil (62 mg, 273 µmol) in 91% yield.

$\mathbf{R}_f$ = 0.25 (petroleum ether/Et_2O = 10:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 5.35 (dd, J = 5.3, 1.6 Hz, 1H, C*H*O(ON)), 3.89 – 3.79 (m, 2H, C*H*$_2$O), 2.04 – 1.71 (m, 4H, 2x CH_2), 1.57 – 1.25 (m, 6H, 3X CH_2), 1.21 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.03 (s, 3H, CH_3).

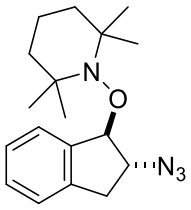
^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 109.6 (t, *C*HO(ON)), 66.7 (s, *C*H_2O), 60.2 (q, *C*$(CH_3)_2$), 58.7 (q, *C*$(CH_3)_2$), 40.1 (s, *C*H_2C$(CH_3)_2$), 39.7 (s, *C*H_2C$(CH_3)_2$), 33.9 (p, *C*H_3), 33.4 (p, *C*H_3), 31.3 (s, *C*H_2), 24.0 (s, *C*H_2), 20.5 (p, *C*H_3), 20.1 (p, *C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[249]

General Procedure C: Photochemical azidooxygenation of alkenes:

A mixture of the alkene (300 µmol, 1.00 eq.), polymer **266** (573 mg, 1.20 mmol, 4.00 eq. based on the effective loading of 2.10 mmol/g resin) and TEMPO (**221**) (93.7 mg, 600 µmol, 2.00 eq.) was stirred under blue LED light in dry CH_2Cl_2 (1.70 mL) at rt under an argon atmosphere. After 20 h, the reaction was terminated by filtration and the resin was washed with CH_2Cl_2. Polymer-bound thiosulfate (**E41**) was added and the reaction mixture was stirred for 10 minutes until the solution was almost colorless. It was then filtered through a pad of cotton, filtered and concentrated under reduced pressure.

(±)-1-(((1*R*,2*R*)-2-Azido-2,3-dihydro-1*H*-inden-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (323)



323
$C_{18}H_{26}N_4O$
MW: 314.43

The title compound was prepared according to general procedure C using indene (**272**). The crude product was purified using flash column chromatography (petroleum ether/Et_2O 40:1) to afford azido-alkoxyamine **323** as a colorless oil (73 mg, 232 µmol) in 77% yield.

$\mathbf{R}_f$ = 0.27 (petroleum ether/Et_2O 40:1).

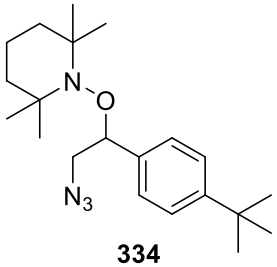
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.57 (d, J = 7.1 Hz, 1H, Ar*H*), 7.30 – 7.20 (m, 3H, Ar*H*), 5.34 (d, J = 4.0 Hz, 1H, C*H*ON), 4.41 (dt, J = 7.1, 4.6 Hz, 1H, C*H*N_3), 3.37 (dd, J = 16.2, 7.2 Hz, ArC*H*H), 2.88 (dd, J = 2.9 Hz, ArCH*H*), 1.57 – 1.34 (m, 6H, 3x CH_2), 1.30 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.05 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 140.6 (q, Ar*C*), 140.2 (q, Ar*C*), 129.0 (t, Ar*C*H), 126.9 (t, Ar*C*H), 126.7 (t, Ar*C*H), 124.8 (t, Ar*C*H), 90.3 (t, *C*HON), 66.8 (t, *C*HN_3), 60.9 (q, *C*$(CH_3)_2$), 60.0 (q, *C*$(CH_3)_2$), 40.4 (s, 2x *C*H_2), 36.8 (s, *C*H_2CHN_3), 34.4 (p, *C*H_3), 33.9 (p, *C*H_3), 20.7 (p, *C*H_3), 17.4 (s, *C*H_2).

IR ν_{max} [cm^{-1}] 2099 ν(N_3).

The analytical data are consistent with those reported in the literature.[250]

1-(2-Azido-1-(4-(*tert*-butyl)phenyl)ethoxy)-2,2,6,6-tetramethylpiperidine (334)



334
$C_{21}H_{34}N_4O$
MW: 358.53

The title compound was prepared according to general procedure C using 4-*tert*-butylstyrene (**325**). The crude product was purified using flash column chromatography (petroleum ether/Et_2O 1:0 → 50:1) to furnish azido-alkoxyamine **334** as a thick colorless oil (71 mg, 198 µmol) in 67% yield.

$\mathbf{R}_f$ = 0.20 (petroleum ether/Et_2O 40:1).

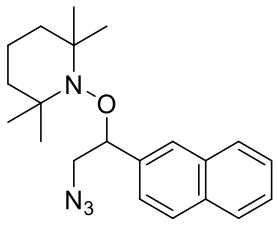
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.35 (d, J = 8.3 Hz, 2H, 2x Ar*H*), 7.26 (d, J = 8.2 Hz, 2H, 2x Ar*H*), 4.81 (dd, J = 6.7, 4.8 Hz, 1H, C*H*ON), 3.77 (dd, J = 12.2, 4.6 Hz, 1H, C*H*HN_3), 3.77 (dd, J = 12.2, 7.0 Hz, 1H, CH*H*N_3), 1.49 – 1.26 (m, 6H, 3x CH_2), 1.32 (s, 12H, *t*Bu-*H*s, CH_3), 1.19 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.72 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 150.9 (q, Ar*C*-CON), 137.6 (q, Ar*C*-*t*Bu), 127.3 (t, 2x Ar*C*H), 125.2 (t, 2x Ar*C*H), 84.6 (t, *C*ON), 60.2 (q, 2x *C*$(CH_3)_2$), 55.3 (s, *C*H_2N_3), 40.6 (s, 2x *C*H_2), 34.7 (p, *C*H_3), 34.5 (p, *C*H_3), 34.1 (p, *C*H_3), 31.5 (p, 3x *C*H_3), 20.5 (p, 2x *C*H_3), 17.3 (s, *C*H_2).

IR ν_{max} [cm^{-1}] 2099 $\nu(N_3)$.

The analytical data are consistent with those reported in the literature.[251]

1-(2-Azido-1-(naphthalen-2-yl)ethoxy)-2,2,6,6-tetramethylpiperidine (335)



335
$C_{21}H_{28}N_4O$
MW: 352.48

The title compound was prepared according to general procedure C using 2-vinylnaphthalene (**326**). The product was purified using flash column chromatography (petroleum ether/Et_2O 40:1) that furnished azido-alkoxyamine **335** as a colorless oil (48 mg, 136 µmol) in 45% yield.

R_f = 0.17 (petroleum ether/Et_2O 40:1).

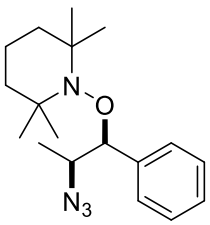
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.88 – 7.83 (m, 3H, Ar*H*), 7.79 (s, 1H, Ar*H*), 7.55 – 7.46 (m, 3H, Ar*H*), 5.00 (dd, J = 6.8, 4.7 Hz, 1H, C*H*ON), 3.83 (dd, J = 12.4, 4.6 Hz, 1H, C*H*HN_3), 3.75 (dd, J = 12.3, 6.9 Hz, 1H, CH*H*N_3), 1.53 – 1.27 (m, 9H, 3x CH_2, CH_3), 1.25 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.68 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 138.9 (q, Ar*C*), 133.3 (q, Ar*C*), 133.2 (q, Ar*C*), 128.2 (t, Ar*C*H), 128.1 (t, Ar*C*H), 127.0 (t, Ar*C*H), 126.9 (t, Ar*C*H), 126.2 (t, Ar*C*H), 126.1 (t, Ar*C*H), 125.4 (t, Ar*C*H), 85.3 (*C*HON), 60.3 (q, 2x *C*$(CH_3)_2$), 55.4 (s, *C*H_2N_3), 40.6 (s, 2x *C*H_2), 34.6 (p, *C*H_3), 34.3 (p, *C*H_3), 20.5 (p, 2x *C*H_3), 17.2 (s, *C*H_2).

IR ν_{max} [cm^{-1}] 2099 $\nu(N_3)$.

The analytical data are consistent with those reported in the literature.[251]

(±)-1-((1*S*,2*S*)-2-Azido-1-phenylpropoxy)-2,2,6,6-tetramethylpiperidine (336)



336
$C_{18}H_{28}N_4O$
MW: 316.45

The title compound was prepared according to general procedure C using (*E*)-prop-1-en-1-ylbenzene (**327**). The crude product was purified using flash column chromatography (petroleum ether/Et_2O 20:1) to furnish azido-alkoxyamine **335** as a colorless oil (46 mg, 146 µmol) in 49% yield.

$\mathbf{R}_f$ = 0.48 (petroleum ether/Et_2O 10:1).

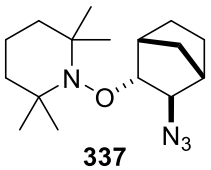
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.34 – 7.27 (m, 5H, 5x Ar*H*), 4.62 (d, J = 3.3 Hz; 1H, C*H*ON), 4.45 (qd, J = 6.9, 3.3 Hz, 1H, C*H*N_3), 1.60 – 1.24 (m, 12H, 2x CH_3, 3x CH_2), 1.04 (s, 3H, CH_3), 0.97 (d, J = 6.9 Hz, 3H, CHN$_3$CH_3), 0.62 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 138.2 (q, Ar*C*), 129.1 (t, 2x Ar*C*), 127.73 (t, Ar*C*H), 127.67 (t, 2x Ar*C*), 90.5 (t, *C*HON), 60.2 (q, 2x *C*$(CH_3)_2$), 59.5 (t, *C*HN_3), 40.7 (s, 2x *C*H_2), 34.4 (p, *C*H_3), 34.2 (p, *C*H_3), 20.74 (p, *C*H_3), 20.65 (p, *C*H_3), 17.21 (p, *C*H_3CHN_3), 17.19 (s, *C*H_2).

IR ν_{max} [cm^{-1}] 2106 ν(N_3).

The analytical data are consistent with those reported in the literature.[251]

(±)-1-(((1*R*,2*R*,3*R*,4*S*)-3-Azidobicyclo[2.2.1]heptan-2-yl)oxy)-2,2,6,6-tetramethylpiperidine (337)



337

$C_{16}H_{28}N_4O$

MW: 292.43

This compound was prepared according to general procedure C using racemic 2-norborene (**328**). The product was then purified using flash column chromatography (petroleum ether/Et_2O 40:1). Azido-alkoxyamine **337** was afforded as a colorless oil (50 mg, 151 µmol) in 57% yield.

$\mathbf{R}_f$ = 0.37 (petroleum ether/Et_2O 40:1).

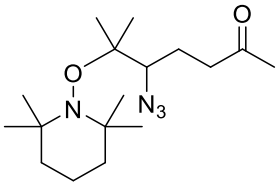
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 3.96 (t, J = 2.2 Hz, 1H, C*H*ON), 3.26 (t, J = 2.3 Hz, 1H, C*H*N_3), 2.58 (brs, 1H), 2.30 (d, J = 4.5 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.68 – 1.09 (m, 23H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 93.0 (t, *C*HON), 70.8 (t, *C*HN_3), 60.1 (q, *C*$(CH_3)_2$), 59.6 (q, *C*$(CH_3)_2$), 42.2 (t, *C*H), 40.9 (t, *C*H), 40.3 (t, 2x *C*H_2), 34.7 (s, *C*H_2), 34.3 (p, *C*H_3), 34.1 (p, *C*H_3), 26.7 (s, *C*H_2), 20.6 (p, *C*H_3), 20.4 (s, *C*H_2), 20.3 (p, *C*H_3), 17.3 (s, *C*H_2).

IR ν_{max} [cm^{-1}] 2091 ν(N_3).

The analytical data are consistent with those reported in the literature.[251]

5-Azido-6-methyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)heptan-2-one (338)



338

$C_{17}H_{32}N_4O_2$

MW: 324.47

This compound was prepared according to general procedure C using racemic 6-methylhept-5-en-2-one (**329**). The product was then purified using flash column chromatography (petroleum

ether/EtOAc 20:1). Azido-alkoxyamine **338** was afforded as a colorless oil (49 mg, 152 µmol) in 51% yield.

$\mathbf{R}_f$ = 0.54 (petroleum ether/EtOAc 10:1).

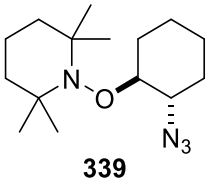
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 3.58 (dd, J = 11.6, 2.0 Hz, 1H, C*H*N_3), 2.68 (ddd, J = 17.7, 8.9, 5.2 Hz, 1H, C*H*HCO), 2.55 (ddd, J = 17.5, 8.5, 6.8 Hz, 1H, CH*H*CO), 2.19 (s, 3H, CH_3CO), 2.11 (dddd, J = 14.1, 9.1, 6.6, 2.2 Hz, 1H, C*H*HCHN_3), 1.57 – 1.42 (m, 6H, 3x CH_2), 1.34 (s, 3H, CH_3), 1.33 – 1.26 (m, 1H, CH*H*CHN_3), 1.24 (s, 3H, CH_3), 1.12 – 1.10 (m, 12H, 4x CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 208.1 (q, *C*=O), 82.2 (q, *C*$(CH_3)_2$ON), 71.2 (t, *C*HN_3), 59.6 (q, *C*$(CH_3)_2$), 59.4 (q, *C*$(CH_3)_2$), 41.1 (s, *C*H_2), 41.0 (s, *C*H_2), 40.9 (s, *C*H_2), 35.04 (p, *C*H_3), 34.96 (p, *C*H_3), 30.0 (p, *C*H_3CO), 24.0 (s, *C*H_2), 23.6 (p, *C*H_3), 22.7 (p, *C*H_3), 21.1 (p, *C*H_3), 20.8 (p, *C*H_3), 17.1 (s, *C*H_2);

IR ν_{max} [cm^{-1}] 2093 ν(N_3).

The analytical data are consistent with those reported in the literature.[250]

(±)-1-(((1*S*,2*S*)-2-Azidocyclohexyl)oxy)-2,2,6,6-tetramethylpiperidine (339)



339

$C_{15}H_{28}N_4O$

MW: 280.42

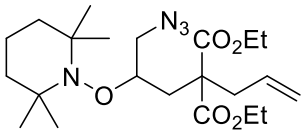
This compound was prepared according to general procedure C using cyclohexene (**277**). The product was then purified using flash column chromatography (petroleum ether/EtOAc 10:1). Azido-alkoxyamine **339** was afforded as a colorless oil (3.0 mg, 10.7 µmol) in 4% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 3.70 (td, J = 14.2, 3.9 Hz, 1H, C*H*ON), 3.35 – 3.30 (m, 1H, C*H*N_3), 2.36 – 2.33 (m, 1H, C*H*HCHN_3), 1.98 (m, 1H, C*H*HCHON), 1.72 – 1.10 (m, 24H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 83.8 (t, *C*HON), 65.0 (t, *C*HN_3), 60.8 (q, *C*$(CH_3)_2$), 59.0 (q, *C*$(CH_3)_2$), 40.5 (s, *C*H_2), 40.3 (s, *C*H_2), 34.6 (p, *C*H_3), 34.4 (p, *C*H_3), 31.0 (s, *C*H_2), 30.7 (s, *C*H_2), 24.2 (s, *C*H_2), 23.8 (s, *C*H_2), 20.6 (p, 2x *C*H_3), 17.3 (s, *C*H_2).

The analytical data are consistent with those reported in the literature.[251]

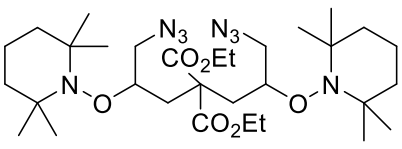
Diethyl 2-allyl-2-(3-azido-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl) malonate (340a) and diethyl 2,2-bis(3-azido-2-((2,2,6,6-tetramethylpiperidin-1-yl) oxy)propyl)malonate (340b)



340a

$C_{22}H_{38}N_4O_5$

MW: 438.57



340b

$C_{31}H_{56}N_8O_6$

MW: 636.84

A mixture of the diethyl 2,2-diallylmalonate (**330**) (74 mg, 0.3 mmol, 1.00 eq.) and polymer **226** (573 mg, 1.20 mmol, 4.00 eq. based on the effective loading of 2.10 mmol/g resin) was stirred in dry CH_2Cl_2 (1.70 mL) at rt under blue LED light irradiation and an argon atmosphere. After 5 days, the reaction was terminated by filtration and the resin was washed with CH_2Cl_2. Polymer-bound thiosulfate (**E41**) was added and the reaction mixture was stirred for 10 minutes until the solution was almost colorless. Then, it was filtered through a pad of cotton, filtered and concentrated under reduced pressure. Purification by semi-preparative HPLC (solvent A: H_2O + 0.1% (v/v) formic acid, solvent B: MeOH + 0.1% (v/v) formic acid; flow rate: 3.0 mL/min; gradient: (t [min]/solvent B [%]): 0/9; 55/100; 80/100) afforded the mono-azidooxygenated product **400a** as a colorless oil (33 mg, 75.2 µmol) in 25% yield and di-azidooxygenated product **400b** as an inseparable mixture of diastereomeres as a colorless oil (11 mg, 17.3 µmol) in 6% yield.

Diethyl 2-allyl-2-(3-azido-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)malonate (340a)

$\mathbf{R}_f$ = 0.32 (petroleum ether/EtOAc = 20:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): 5.80 (m, 1H, C*H*=CH_2), 5.14 – 5.08 (m, 2H, CH_2=CH), 4.27 – 4.09 (m, 5H, 2x OC$H_2$$CH_3$, C*H*$HN_3$), 3.95 (tt, J = 13.1; 3.3 Hz, C*H*ON, 1H), 3.05 (dd, J = 11.8; 8.7 Hz, 1H, C*H*HN_3), 2.89 (dd, J = 14.3; 6.7 Hz, 1H, C*H*HCH=CH_2), 2.73 (dd, J = 14.4; 8.0 Hz, 1H, C*H*HCH=CH_2), 2.34 (dd, J = 15.0; 3.2 Hz, 1H, C*H*HCON), 2.23 (dd, J = 15.0; 8.7 Hz, 1H, C*H*HCON), 1.61 – 1.29 (m, 6H, 3x *C*H_2) 1.24 (q, J = 6.8 Hz, 3H, C$H_3$$CH_2$), 1.16 (s, 3H, C$H_3$), 1.13 (s, 3H, C$H_3$), 1.01 (s, 6H, 2x C$H_3$).

^{13}C-NMR ($CDCl_3$, 100 MHz): 171.2 (q, *C*O_2Et), 171.1 (q, *C*O_2Et), 132.7 (t, *C*H=CH_2), 119.1 (s, *C*H2=CH), 77.0 (t, *C*H-ON), 61.6 (s, *C*H_2O), 61.4 (s, *C*H_2O), 60.7 (q, *C*$(CH_3)_2$), 59.4 (q, *C*$(CH_3)_2$), 56.3 (q, *C*$(CO_2Et)_2$), 53.5 (s, *C*H_2N_3), 40.7 (s, *C*H_2-C$(CH_3)_2$), 40.2 (s, *C*$H_2C(CH_3)_2$), 37.2 (s, *C*H_2CH=CH_2), 35.5 (s, *C*H_2CON), 34.3 (p, *C*H_3), 33.7 (p, *C*H_3), 21.0 (p, *C*H_3), 20.8 (p, *C*H_3), 17.3 (s, *C*H_2), 14.2 (p, *C*H_3CH_2O), 14.1 (p, *C*H_3CH_2O).

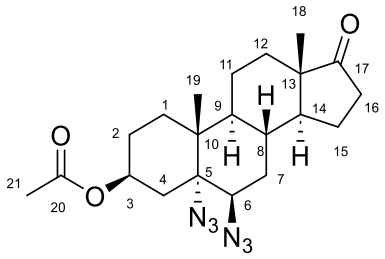
HRMS (ESI^+) *m/z* calculated for $C_{22}H_{38}N_4O_5Na$ $[M+Na]^+$ 461.2740; found 461.2740.

Diethyl 2,2-bis(3-azido-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)malonate (340b)

$\mathbf{R}_f$ = 0.32 (petroleum ether/EtOAc = 20:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): 4.39 (dd, J = 11.4, 3.1 Hz), 4.27 (dq, J = 10.8, 7.0 Hz, 1H), 4.18 (p, J = 7.0 Hz, 2H), 4.11 (t, J = 7.1 Hz, 1H), 4.08 – 3.97 (m, 3H) (2x C*H*NO, CH_2N_3, 2x OC*H*2CH3), 3.25 (dd, J = 12.1, 7.1 Hz, 1H, C*H*HN_3), 3.05 (dd, J = 11.4, 9.8 Hz, 1H, C*H*HN_3), 1.50 – 1.30 (m, 4H, 2x CH_2C(CO_2Et)), 1.60 – 1.38 (m, 12H, 6x CH_2), 1.25 (t, J = 7.1 Hz, 6H, 2x C$H_3$$CH_2$), 1.22 (s, 3H, C$H_3$), 1.20 (s, 3H, C$H_3$), 1.15 (s, 3H, C$H_3$), 1.11 (s, 3H, C$H_3$), 1.03 (s, 6H, 2x C$H_3$), 0.98 (s, 3H, C$H_3$), 0.96 (s, 3H, C$H_3$).

((3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-5,6-Diazido-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (343)



343

$C_{21}H_{30}N_6O_3$

MW: 414.51

The title compound was prepared according to general procedure C using 3-(acetoxy)-androst-5-en-17-one (**332**) as starting alkene. The crude product was purified using flash column chromatography (petroleum ether/EtOAc = 20:1 ⟶ 3:1) to furnish the bis-azido steroid **343** as a colorless solid (61 mg, 150 µmol) in 50% yield.

R$_f$ = 0.35 (petroleum ether/EtOAc = 5:1).

mp = 130 °C (decomposition).

[α]$_D^{22.4}$ = – 53.8° (*c* 0.5, $CHCl_3$).

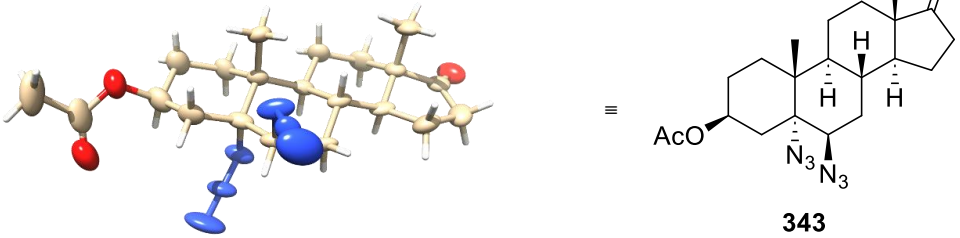
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 5.03 (dp, J = 16.7, 5.4 Hz, 1H, *H*-3), 3.63 (s, 1H, *H*-6), 2.47 (dd, J = 18.9, 9.1 Hz, 1H, *H*-16), 2.23 (dd, J = 13.5, 11.4 Hz, 1H, *H*-4), 2.11 (dd, J = 19.0, 9.4 Hz, 1H, *H*-16'), 2.05 (s, 3H, *H*-21), 1.99 – 1.95 (m, 2H, *H*-4', *H*-15), 1.93 – 1.83 (m, 3H, *H*-2/7/7'), 1.82 – 1.77 (m, 2H, *H*-8, *H*-12), 1.60 – 1.50 (m, 4H, *H*-1, *H*-2', *H*-11. *H*-15'), 1.41 – 1.33 (m, 3H, *H*-1', *H*-9, *H*-14), 1.31 – 1.25 (m, 2H, *H*-11', *H*-12'), 1.18 (s, 3H, *H*-19), 0.87 (s, 3H, *H*-18).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 220.4 (q, *C*-17), 170.6 (q, *C*-20), 69.8 (q, *C*-5), 69.7 (t, *C*-3), 63.0 (t, *C*-6), 50.6 (t, *C*-14), 47.9 (q, *C*-13), 45.6 (t, *C*-9), 38.7 (q, *C*-10), 35.8 (s, *C*-16), 33.3 (s, *C*-4), 32.5 (s, *C*-1), 31.4 (s, *C*-12), 30.7 (s, *C*-7), 30.5 (t, *C*-8), 26.4 (s, *C*-2), 21.8 (s, *C*-15), 21.4 (p, *C*-21), 20.3 (s, *C*-11), 17.0 (p, *C*-19), 14.0 (p, *C*-18).

IR ν_{max} [cm^{-1}] 2099 ν(N_3).

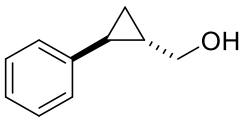
HRMS (ESI$^+$) *m/z* calculated for $C_{21}H_{30}N_6O_3Na$ $[M+Na]^+$ 437.2277; found 437.2274.

Determination of the relative configuration of compound **343** was confirmed by X-ray structure analysis using a BRUKER SMART X2S benchtop crystallographic system. The data are deposited at the Cambridge Crystallographic Data Center (CCDC 1985449).



343

(±)-((1*S*,2*S*)-2-Phenylcyclopropyl)methanol (E42)



E42
$C_{10}H_{12}O$
MW: 148.21

Cinnamyl alcohol (671 mg, 5.00 mmol, 1.00 eq.) was dissolved in anhydrous CH_2Cl_2 (12.5 mL) under Ar atmosphere. The solution was cooled to 0 °C, Et_2Zn (1.00 M in hexane, 6.25 mL, 6.25 mmol, 1.25 eq.) was slowly added and the mixture was stirred for 30 min at 0 °C. In a second flask, Et_2Zn (1.00 M in hexane, 6.25 mL, 6.25 mmol, 1.25 eq.) was added to CH_2I_2 (806 µL, 10.0 mmol, 2.00 eq.) in anhydrous CH_2Cl_2 (50.0 mL) under Ar atmosphere and stirred for 30 min at 0 °C. The mixture of the first flask was added to the second flask at 0 °C, the resulting mixture was allowed to warm up to rt and stirred overnight. Then, NH_4Cl solution (aq., sat., 50.0 mL) was added until an emulsion formed. Subsequently, a few drops of HCl (2.00 M in H_2O) were added. The mixture was extracted with CH_2Cl_2 (3x 50.0 mL). The combined organic layers were washed with NaCl solution (aq., sat., 30.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain alcohol **E42** as a colorless oil (742 mg, 5.00 mmol) in quantitative yield.

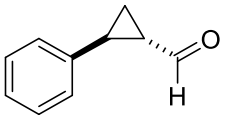
$\mathbf{R}_f$ = 0.17 (petroleum ether/EtOAc = 5:1)

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.27 (t, $\mathcal{J}$ = 7.6 Hz, 2H, 2x Ar*H*), 7.16 (t, J = 7.4 Hz, 1H, Ar*H*), 7.08 (d, $\mathcal{J}$ = 6.9 Hz, 1H, Ar*H*), 3.70 – 3.56 (m, 2H, C*H*$_2$OH), 1.83 (dt, $\mathcal{J}$ = 9.3, 4.9 Hz, 1H, PhC*H*), 1.61 (s, 1H, O*H*), 1.47 (dtdd, $\mathcal{J}$ = 8.3, 6.7, 5.6, 4.4 Hz, 1H, PhCHC*H*), 0.96 (ddt, $\mathcal{J}$ = 15.1, 8.7, 5.1 Hz, 2H, C*H*$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 142.5 (q, Ar*C*), 128.5 (t, 2x Ar*C*), 125.9 (t, 2x Ar*C*),125.8 (t, Ar*C*H), 66.7 (s, *C*H$_2$OH), 25.4 (t, PhCH*C*H), 21.4 (t, Ph*C*H), 14.0 (s, *C*H$_2$).

The analytical data are consistent with those reported in the literature.[252]

(±)-(1*S*,2*S*)-2-Phenylcyclopropane-1-carbaldehyde (E43)



E43
$C_{10}H_{10}O$
MW: 146.19

A mixture of **E42** (741 mg, 5.00 mmol, 1.00 eq.) and pyridinium chlorochromate (2.16 g, 10.0 mmol, 2.00 eq.) in dry CH_2Cl_2 (62.5 mL) was allowed to stir at rt for 3 h. Then, the reaction mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. After purification by column chromatography (petroleum ether/EtOAc = 10:1) aldehyde **E43** was isolated as colorless oil (198 mg, 1.35 mmol) in 27% yield.

$\mathbf{R}_f$ = 0.57 (petroleum ether/EtOAc = 5:1)

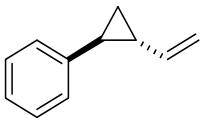
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 9.33 (d, $\mathcal{J}$ = 4.6 Hz, 1H, C*H*O), 7.30 (t, $\mathcal{J}$ = 7.4 Hz, 2H, 2x Ar*H*), 7.23 (t, $\mathcal{J}$ = 7.3 Hz, 1H, Ar*H*), 7.12 (d, $\mathcal{J}$ = 6.9 Hz, 1H, Ar*H*), 2.63 (ddd, $\mathcal{J}$ = 9.2, 6.7, 4.0 Hz, 1H, PhC*H*), 2.17

(dt, J = 13.2, 4.7 Hz, 1H, PhCHC*H*), 1.74 (dt, J = 9.2, 5.1 Hz, 1H, C*H*H), 1.54 (ddd, J = 8.2, 6.7, 4.9 Hz, 1H, CH*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 199.8 (t, *C*HO), 139.1 (q, Ar*C*), 128.7 (t, 2x Ar*C*), 127.0 (t, Ar*C*H), 126.4 (t, 2x Ar*C*), 33.9 (t, PhCH*C*H), 26.7 (t, Ph*C*H), 16.6 (s, *C*H_2).

The analytical data are consistent with those reported in the literature.[253]

(±)-((1*S*,2*R*)-2-Vinylcyclopropyl)benzene (344)



344
$C_{11}H_{12}$
MW: 144.22

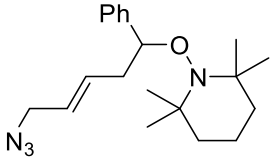
To a solution of methyltriphenylphosphonium bromide (457 mg, 1.28 mol, 1.10 eq.) in dry THF (2.91 mL) was added *n*BuLi (2.50 M in hexanes, 512 µL, 1.28 mmol, 1.10 eq.) dropwise at −78 °C. The resulting mixture was stirred at 0 °C for 2 h. Then, it was cooled to −78 °C followed by the slow addition of a solution of aldehyde **E43** (170 mg, 1.16 mmol, 1.00 eq.) in dry THF (2.91 mL). The resulting mixture was allowed to warm up to rt and was stirred overnight, terminated by the addition of NH_4Cl solution (aq., sat., 5.00 mL) and then extracted with EtOAc (3x 10.0 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether) to give product **344** as a colorless oil (137 mg, 950 µmol) in 82% yield.

$\mathbf{R}_f$ = 0.62 (petroleum ether).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.27 (t, J = 7.2 Hz, 2H, 2x Ar*H*), 7.16 (t, J = 7.4 Hz, 1H, Ar*H*), 7.08 (d, J = 6.7 Hz, 1H, Ar*H*), 5.55 (ddd, J = 17.0, 10.3, 8.5 Hz, 1H, C*H*=CH_2), 5.12 (d, J = 17.0 Hz, 1H, C*H*H=CH), 4.95 (dd, J = 10.3, 1.5 Hz, 1H, CH*H*=CH), 1.94 (ddd, J = 8.8, 5.6, 4.3 Hz, 1H, PhC*H*), 1.71 (sep, J = 4.5 Hz, 1H, PhCHC*H*), 1.21 (dt, J = 8.5, 5.4 Hz, 1H, PhCHC*H*H), 1.12 (dt, J = 8.7, 5.3 Hz, 1H, PhCHCH*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 142.8 (q, Ar*C*), 140.8 (t, *C*H=CH_2), 128.5 (t, 2x Ar*C*), 125.83 (t, Ar*C*H), 125.76 (t, Ar*C*H), 112.7 (s, *C*H_2=CH), 27.5 (t, Ph*C*H), 25.4 (t, *C*HCH=CH_2), 16.9 (s, *C*H_2(CH_2)$_2$).
The analytical data are consistent with those reported in the literature.[253]

(*E*)-1-((5-Azido-1-phenylpent-3-en-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (345)



345
$C_{20}H_{30}N_4O$
MW: 342.49

The title compound was prepared according to general procedure C using (±)-((1*S*,2*R*)-2-vinylcyclopropyl)benzene (**344**) as starting alkene. The crude product was purified using semi-

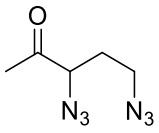
preparative HPLC (solvent A: H_2O + 0.1% (*v/v*) formic acid, solvent B: MeCN + 0.1% (*v/v*) formic acid; flow rate: 3.0 ml/min; gradient: (*t* [min]/solvent B [%]): 0/0; 60/100; 80/100; t_R = 33.0 min) to afford product **345** as a colorless oil (3.0 mg, 8.76 µmol) in 3% yield

^{1}H-NMR (CD_3CN, 600 MHz): δ [ppm] 7.38 – 7.24 (m, 5H, 5x Ar*H*), 5.53 (dt, $\mathcal{J}$ = 15.2, 7.1 Hz, 1H, *C*HCH$_2$N$_3$), 5.44 (dt, $\mathcal{J}$ = 15.0, 6.6 Hz, 1H, C*H*CH$_2$CHON), 4.71 (dd, $\mathcal{J}$ = 9.3, 4.2 Hz, 1H, C*H*NO), 3.60 (d, $\mathcal{J}$ = 6.4 Hz, 2H, C*H*$_2$N$_3$), 2.92 – 2.87 (m, 1H, CH(NO)C*H*H), 2.65 – 2.60 (m, 1H, CH(NO)CH*H*), 1.62 – 1.36 (m, 6H, 3x C*H*$_2$), 1.32 (s, 3H, C*H*$_3$), 1.18 (s, 3H, C*H*$_3$), 1.01 (s, 3H, C*H*$_3$), 0.59 (s, 3H, C*H*$_3$).

^{13}C-NMR (CD_3CN, 150 MHz): 143.8 (q, Ar*C*), 133.0 (t, *C*HCH$_2$N$_3$), 131.9 (t, *C*HCH$_2$Ph), 128.8 (t, 3x Ar*C*), 128.2 (t, Ar*C*H), 126.6 (t, Ar*C*H), 87.4 (t, *C*HON), 60.7 (q, *C*(CH$_3$)$_2$), 60.3 (q, *C*(CH$_3$)$_2$), 53.1 (s, *C*H$_2$N$_3$), 41.2 (s, *C*H$_2$), 39.5 (s, *C*H$_2$), 34.8 (p, *C*H$_3$), 34.5 (p, *C*H$_3$), 20.6 (p, 2x *C*H$_3$), 17.8 (s, *C*H$_2$).

The analytical data are consistent with those reported in the literature.[250]

3,5-Diazidopentan-2-one (347)



347
$C_5H_8N_6O$
MW: 168.16

A mixture of 1-cyclopropylethanol (**346**) (112 µL, 1.20 mmol, 1.00 eq.) and polymer **266** (1.13 g, 4.80 mmol, 4.00 eq. based on the effective loading of 2.10 mmol/g resin) in CH_2Cl_2 (6.80 mL) was stirred under blue LED light at rt under an Ar atmosphere. After 20 h, the reaction was terminated by filtration and the resin was washed with CH_2Cl_2. Polymer-bound thiosulfate (**E41**) was added and the reaction mixture was stirred for 10 minutes until the solution was almost colorless. Then, it was filtered through a pad of cotton, filtered and concentrated under reduced pressure. The product mixture was purified using flash column chromatography (petroleum ether/CH_2Cl_2 = 3:1 ⟶ 1:1) to obtain 3,5-diazidopentane-2-one (**347**) as a pale-yellow oil (72 mg, 428 µmol) in 36% yield.

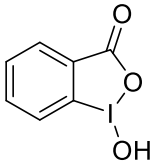
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 4.00 (dd, $\mathcal{J}$ = 8.9, 4.6 Hz, 1H, C*H*N$_3$), 3.53 – 3.43 (m, 2H, C*H*$_2$N$_3$), 2.27 (s, 3H, C*H*$_3$), 2.11 – 2.00 (m, 1H, C*H*H), 1.89 – 1.80 (m, 1H, CH*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 204.4 (q, *C*=O), 65.9 (p, *C*HN$_3$), 47.7 (s, *C*H$_2$N$_3$), 30.0 (s, CH$_2$), 27.2 (p, *C*H$_3$).

IR ν_{max} [cm^{-1}] 2099 ν(N$_3$).

GC-MS (EI) *m/z* calcd. for $C_5H_8N_2O$ $[M-2N_2]^+$ 112.1; found 112.1.

1-Hydroxy-1λ^3-benzo[d][1,2]iodaoxol-3(1*H*)-one (E44)



E44
$C_7H_5IO_3$
MW: 264.02

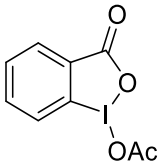
$NaIO_4$ (7.24 g, 33.8 mmol, 1.05 eq.) and 2-iodobenzoic acid (8.00 g, 32.2 mmol, 1.00 eq.) were suspended in AcOH (30 wt%, aq., 48.0 mL). The mixture was stirred vigorously and heated under refluxing conditions for 4 h. Then, the reaction mixture was diluted with cold water (180 mL) and allowed to cool to rt. After 1 h, the crude product was collected by filtration. The precipitate was washed with ice water (3× 20.0 mL) and acetone (3× 20.0 mL), and then air-dried in the dark to give the desired product as a colorless solid (8.30 g, 31.4 mmol) in 97% yield.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.06 (bs, 1H, O*H*), 8.01 (dd, J = 7.5, 1.5 Hz, 1H, Ar*H*), 7.94 (dt, J = 7.6, 1.3 Hz, 1H, Ar*H*), 7.84 (d, J = 7.9 Hz, 1H, Ar*H*), 7.69 (dt, J = 7.4, 0.8 Hz, 1H, Ar*H*).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ [ppm] 167.9 (q, *C*=O), 134.6 (t, Ar*C*H), 131.5 (q, Ar*C*), 131.2 (t, Ar*C*H), 130.4 (t, Ar*C*H), 126.3 (t, Ar*C*H), 120.5 (1, Ar*C*).

The analytical data are in accordance with those reported in the literature.[254]

3-Oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (E45)



E45
$C_9H_7IO_4$
MW: 306.06

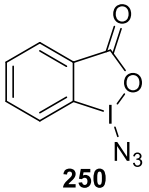
A suspension of iodaoxolone **E44** (3.00 g, 11.3 mmol, 1.00 equiv.) Ac_2O (10.0 mL) was heated under refluxing conditions until the solution turned clear (30 min). Then, the mixture was left to cool to rt and colorless crystals started to form. The crystallization was continued at -18 °C. The crystals were then collected by filtration and dried overnight under high vacuum to give the acetate **E45** as a colorless crystalline solid (3.26 g, 10.6 mmol) in 94% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.19 (d, J = 6.9 Hz, 1H, Ar*H*), 7.97 (d, J = 8.3 Hz, 1H, Ar*H*), 7.90 (dt, J = 7.7, 1.2 Hz, 1H, Ar*H*), 7.32 (t, J = 7.3 Hz, 1H, Ar*H*), 2.23 (s, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 176.4 (q, *C*=O), 168.2 (q, *C*=O), 136.2 (t, Ar*C*H), 133.1 (t, Ar*C*H), 129.3 (t, Ar*C*H), 129.0 (q, Ar*C*), 118.4 (q, Ar*C*), 20.3 (p, *C*H_3).

The analytical data are in accordance with those reported in the literature.[254]

1-Azido-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (ZHDANKIN's reagent, 250)



250

$C_7H_4IN_3O_2$

MW: 289.03

To a suspension of benziodoxolone **E45** (8.30 g, 27.1 mmol, 1.00 eq.) in CH_2Cl_2 (16.4 mL) was treated with $TMSN_3$ (5.33 mL, 40.7 mmol, 1.50 eq.) followed by TMSOTf (24.5 µL, 136 µmol, 10 mol%) at 0 °C. After stirring for 1 h at rt, the resulting solid was filtered, washed with hexane (20.0 mL) and CH_2Cl_2 (20.0 mL) and dried under reduced pressure to obtain ZHDANKIN's reagent (**250**) as a pale-yellow solid (5.59 g, 19.3 mmol) in 71% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.32 (d, J = 7.6 Hz, 1H, Ar*H*), 8.01 – 7.96 (m, 2H, 2x Ar*H*), 7.80 – 7.77 (m, 1H, Ar*H*).

^{13}C-NMR ($CDCl_3$/CD_3CN 10:1, 100 MHz): δ [ppm] 136.1 (t, ArC*H*), 133.1 (t, ArC*H*), 129.6 (q, ArC), (t, ArC*H*), 126.7 (t, ArC*H*), 117.9 (q, ArC). (Peak for *C*=O is not visible in the ^{13}C NMR spectrum due to the low solubility of compound **250** in $CDCl_3$).

The analytical data are in accordance with those reported in the literature.[254]

Caution: ZHDANKIN's reagent (**250**) shows a high shock and friction sensitivity and should be handled with care.[255]

General Procedure D: Selective oxidation of secondary alcohols using $PhI(OAc)_2$, $TMSN_3$ and Et_4PBr under blue LED light irradiation

A suspension of $PhI(OAc)_2$ (291 mg, 900 µmol, 3.00 eq.) in dry DCE (12.0 mL) was cooled to −25 °C under an argon atmosphere. Et_4PBr (239 mg, 1.05 mmol, 3.50 eq.) was added and stirring continued for 30 min at −25 °C. $TMSN_3$ (236 µL, 1.81 mmol, 6.00 eq.) was added, followed by water (32.5 µL, 1.81 mmol, 6.00 eq.), and the mixture stirred for additional 30 min at −25 °C. Then, the alcohol (300 µmol, 1.00 eq.) was added and the mixture irradiated with blue LED light and allowed to warm to 0 °C over a period of 1 h. Subsequently, the reaction was terminated by addition of $Na_2S_2O_3$ solution (aq., sat.). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product.

General Procedure E: Selective oxidation of secondary alcohols using $PhI(OAc)_2$, $TMSN_3$ and Et_4PBr without LED light irradiation

A solution of the alcohol (300 µmol, 1.00 eq.) in DCE (3.75 mL) was treated with $TMSN_3$ (314 µL, 2.40 mmol, 8.00 eq.), Et_4PBr (136 mg, 600 µmol, 2.00 eq.) and water (216 µL, 12.0 mmol, 40.0 eq.) at room temperature. Then, $PhI(OAc)_2$ (290 mg, 900 µmol, 3.00 eq.) was added portionwise over 30 min. When the solid was added, nitrogen formation and a yellow coloration of the solution became apparent, which disappeared after a few minutes. After complete addition, the mixture was stirred for additional 30 min before the reaction was terminated by the addition of $Na_2S_2O_3$ solution (aq., sat.). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x). The combined

organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product.

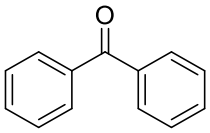
General Procedure F: Selective oxidation of secondary alcohols using Zhdankin's reagent and Et_4PBr under blue LED light irradiation

A solution of the alcohol (300 µmol, 1.00 eq.) in DCE (6.00 mL) was treated with 1-azido-1,2-benziodoxol-3(1*H*)-one (522 mg, 1.81 mmol, 6.00 eq.) and Et_4PBr (273 mg, 1.20 mmol, 4.00 eq.) at –25 °C under an argon atmosphere. Then, the mixture irradiated with blue LED light and allowed to warm to 0 °C over a period of 1 h. Subsequently, the reaction was terminated by addition of $Na_2S_2O_3$ solution (aq., sat.) and K_2CO_3 solution (aq., 10 wt%). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product.

General Procedure G: Selective oxidation of secondary alcohols using Zhdankin's reagent and Et_4PBr without LED light irradiation

A suspension of the alcohol (300 µmol, 1.00 eq.) and 1-azido-1,2-benziodoxol-3(1*H*)-one (390 mg, 1.35 mmol, 4.50 eq.) in DCE (3.75 mL) was treated with and Et_4PBr (204 mg, 900 µmol, 3.00 eq.) at room temperature under an argon atmosphere. Then, the mixture was stirred at 50 °C for 1 h, during which time the formation of nitrogen bubbles can be observed. Subsequently, the reaction was terminated by addition of $Na_2S_2O_3$ solution (aq., sat.) and K_2CO_3 solution (aq., 10 wt%). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product.

Benzophenone (361a)



361a
$C_{13}H_{10}O$
MW: 182.22

This compound was prepared according to general procedure D using 1-phenyl-1,2-ethanediol. The product was then purified using flash column chromatography (petroleum ether/EtOAc = 19:1). Ketone **361a** was collected as a colorless solid (54.1 mg, 297 µmol) in 99% yield.

This compound was also prepared according to general procedure F. In this case, ketone **361a** (54.5 mg, 299 µmol) was afforded in quantitative yield.

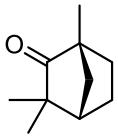
$\mathbf{R}_f$ = 0.29 (petroleum ether/EtOAc = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.81 (dd, J = 8.3, 1.4 Hz, 2H, 2x Ar*H*), 7.63 – 7.55 (m, 1H, Ar*H*), 7.51 (tt, J = 6.5, 1.3 Hz, 2H, 2x Ar*H*).

^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] 196.9 (q, *C*=O), 137.7 (q, Ar*C*), 132.5 (t, Ar*C*H), 130.2 (t, 2x Ar*C*H), 128.4 (t, 2x Ar*C*H).

The analytical data are in accordance with those reported in the literature.[209]

(*1R*,4*S*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one (361b)



361b
$C_{10}H_{16}O$
MW: 152.24

This compound was prepared according to general procedure F using (+)-fenchol. The product was then purified using flash column chromatography (petroleum ether/EtOAc = 30:1 ⟶ 9:1). Ketone **361b** was collected as a colorless oil (20.3 mg, 133 µmol) in 45% yield.

$\mathbf{R}_f$ = 0.47 (toluene/EtOAc = 9:1).

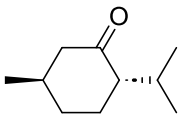
$[\alpha]_D^{27}$ = −41.5° (*c* 1.1, acetone), {Lit. $[\alpha]_D^{20}$ = −44° (*c* 1.0, hexane)[256]}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 2.13 (bs, 1H, C*H*), 1.82 – 1.67 (m, 3H, O=CCCH_2CH/ H_2CH_2CCH), 1.59 – 1.51 (m, 2H, O=CCCH_2CH_2/O=CCCH_2CH), 1.42 – 1.34 (m, 1H, O=CCCH_2CH_2), 1.14 (s, 3H, CH_3), 1.03 (s, 6H, (CH_3)$_2$).

^{13}C-NMR ($CDCl_3$, 101 MHz): δ [ppm] 223.6 (q, *C*=O), 54.3 (q, O=C*C*CH_2), 47.5 (q, *C*(CH_3)$_2$), 45.5 (t, *C*H), 41.8 (s, C*C*H_2CH), 32.0 (s, O=CC*C*H_2CH_2), 25.1 (s, H_2CH_2*C*CH), 23.5 (p, (*C*H_3)$_2$), 21.9 (p, (*C*H_3)$_2$), 14.8 (p, *C*H_3).

The analytical data are in accordance with those reported in the literature.[257]

(2*S*,5*R*)-2-Isopropyl-5-methylcyclohexan-1-one (361c)



361c
$C_{10}H_{18}O$
MW: 154.25

This compound was prepared according to general procedure F using (−)-menthol. The product was then purified using flash column chromatography (petroleum ether/EtOAc = 20:1). Ketone **361c** was collected as a colorless oil (21.1 mg, 137 µmol) in 45% yield.

$\mathbf{R}_f$ = 0.54 (petroleum ether/EtOAc = 9:1).

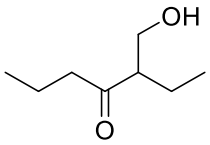
$[\alpha]_D^{27}$ = −28.4° (*c* 0.54, $CHCl_3$) {Lit. $[\alpha]_D^{20}$ = −23.1° (*c* 5.18, $CHCl_3$)[258]}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 2.33 (ddd, $\mathcal{J}$ = 12.9, 3.9, 2.2 Hz, 1H, H_2CC=O), 2.16 – 1.79 (m, 6H, H_2CC=O / *H*CC=O / HCCH_2CH_2 / *H*CCH$_3$ / *H*C(CH$_3$)$_2$ / HCCH_2CH_2), 1.43 – 1.22 (m, 2H, HCCH_2CH_2), 0.99 (d, $\mathcal{J}$ = 6.2 Hz, 3H, CH_3), 0.89 (d, $\mathcal{J}$ = 6.8 Hz, 3H, (CH_3)$_2$), 0.83 (d, $\mathcal{J}$ = 6.8 Hz, 3H, (CH_3)$_2$).

^{13}C-NMR ($CDCl_3$, 101 MHz): δ [ppm] 212.6 (q, *C*=O), 56.0 (t, H*C*C=O), 51.0 (s, H_2*C*C=O), 35.6 (s, H$_3$CCH*C*H$_2$CH$_2$), 34.1 (t, H$_3$C*C*H), 28.0 (t, H*C*(CH$_3$)$_2$, 26.0 (s, H$_3$CCH*C*H$_2$CH$_2$), 22.4 (p, *C*H$_3$), 21.3 (p, (*C*H$_3$)$_2$), 18.8 (p, (*C*H$_3$)$_2$).

The analytical data are in accordance with those reported in the literature.[259]

3-(Hydroxymethyl)heptan-4-one (319)



319
$C_8H_{16}O_2$
MW: 144.21

This compound was prepared according to general procedure F using 2-ethylhexane-1,3-diol. The product was then purified using flash column chromatography (petroleum ether/EtOAc = 3:1). Ketone **319** was collected as a colorless oil (25.1 mg, 174 µmol) in 58% yield.

This compound was also prepared according to general procedure G. In this case, ketone **319** (23.1 mg, 160 µmol) was afforded in 53% yield.

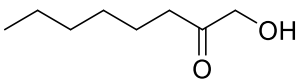
$\mathbf{R}_f$ = 0.48 (petroleum ether/EtOAc = 1:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 3.79 (dd, $\mathcal{J}$ = 11.0, 7.3 Hz, 1H, H_2COH), 3.69 (dd, $\mathcal{J}$ = 11.1, 4.0 Hz, 1H, H_2COH), 2.61 (qd, $\mathcal{J}$ = 11.5, 4.1 Hz, 1H, C*H*), 2.47 (t, $\mathcal{J}$ = 7.2 Hz, 2H, O=CCH_2), 2.13 (br, 1H, O*H*), 1.71 – 1.47 (m, 4H, H_3CCH_2), 0.91 (td, $\mathcal{J}$ = 11.1, 4.4 Hz, 6H, H_3CCH$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] 215.3 (q, *C*=O), 62.6 (s, H_2*C*OH), 55.1 (t, O=C*C*H), 44.9 (s, O=C*C*H$_2$), 21.4 (s, H_3C*C*H$_2$CH), 17.0 (s, H_3C*C*H$_2$CH$_2$), 13.9 (p, H_3*C*CH$_2$CH$_2$), 12.0 (p, H_3*C*CH$_2$CH).

The analytical data are in accordance with those reported in the literature.[209]

1-Hydroxyoctan-2-one (359)



359
$C_8H_{16}O_2$
MW: 144.21

This compound was prepared according to general procedure D using octane-1,2-diol. The product was then purified using flash column chromatography (petroleum ether/EtOAc = 3:1). Ketone **359** was collected as a colorless oil (13.8 mg, 95.7 µmol) in 32% yield.

This compound was also prepared according to general procedure E. In this case, ketone **359** (22.0 mg, 153 µmol) was afforded in 51% yield.

This compound was also prepared according to general procedure F. In this case, ketone **359** (29.8 mg, 207 µmol) was afforded in 69% yield.

This compound was also prepared according to general procedure G. In this case, ketone **359** (28.1 mg, 195 µmol) was afforded in 65% yield.

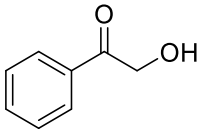
$\mathbf{R}_f$ = 0.54 (petroleum ether/EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 4.24 (s, 2H, H_2COH), 3.00 (br, 1H, O*H*), 2.40 (t, $\mathcal{J}$ = 7.5 Hz, 1H, O=CCH$_2$CH_2), 1.66 – 1.59 (m, 2H, O=CCH_2CH$_2$), 1.33 – 1.25 (m, 6H, H_3C(CH_2)$_3$), 0.87 (t, $\mathcal{J}$ = 6.6 Hz, 3H, H_3CCH$_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] 210.1 (q, *C*=O), 68.2 (s, H_2*C*OH), 38.6 (s, O=C*C*$H_2$$CH_2$), 31.6 (s, CH_3CH_2*C*H_2), 29.0 (s, $CH_3CH_2CH_2$*C*H_2), 23.8 (s, *C*H_2CH_2C=O), 22.6 (s, CH_3*C*H_2), 14.1 (p, *C*H_3).

The analytical data are in accordance with those reported in the literature.[260]

2-Hydroxy-1-phenylethan-1-one (363)



363
$C_8H_8O_2$
MW: 136.15

This compound was prepared according to general procedure D using 1-phenyl-1,2-ethanediol. The product was then purified using flash column chromatography (petroleum ether/EtOAc = 3:1). Ketone **363** was collected as a colorless solid (36.1 mg, 265 µmol) in 88% yield.

This compound was also prepared according to general procedure F. In this case, ketone **363** (39.1 mg, 287 µmol) was afforded in 96% yield.

This compound was also prepared according to general procedure G. In this case, ketone **363** (29.3 mg, 216 µmol) was afforded in 72% yield.

$\mathbf{R}_f$ = 0.48 (petroleum ether/EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.93 (dd, $\mathcal{J}$ = 8.4, 1.4 Hz, 2H, 2x Ar*H*), 7.63 (ddt, $\mathcal{J}$ = 8.0, 6.9, 1.3 Hz, 1H, Ar*H*), 7.51 (ddd, $\mathcal{J}$ = 8.0, 6.7, 1.2 Hz, 2H, 2x Ar*H*), 4.88 (s, 2H, CH_2OH), 3.51 (br, 1H, O*H*).

^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] 198.5 (q, *C*=O), 134.5 (t, Ar*C*H), 133.5 (q, Ar*C*), 129.1 (t, 2x Ar*C*H), 127.9 (t, 2x Ar*C*H), 65.6 (s, *C*H_2OH).

The analytical data are in accordance with those reported in the literature.[261]

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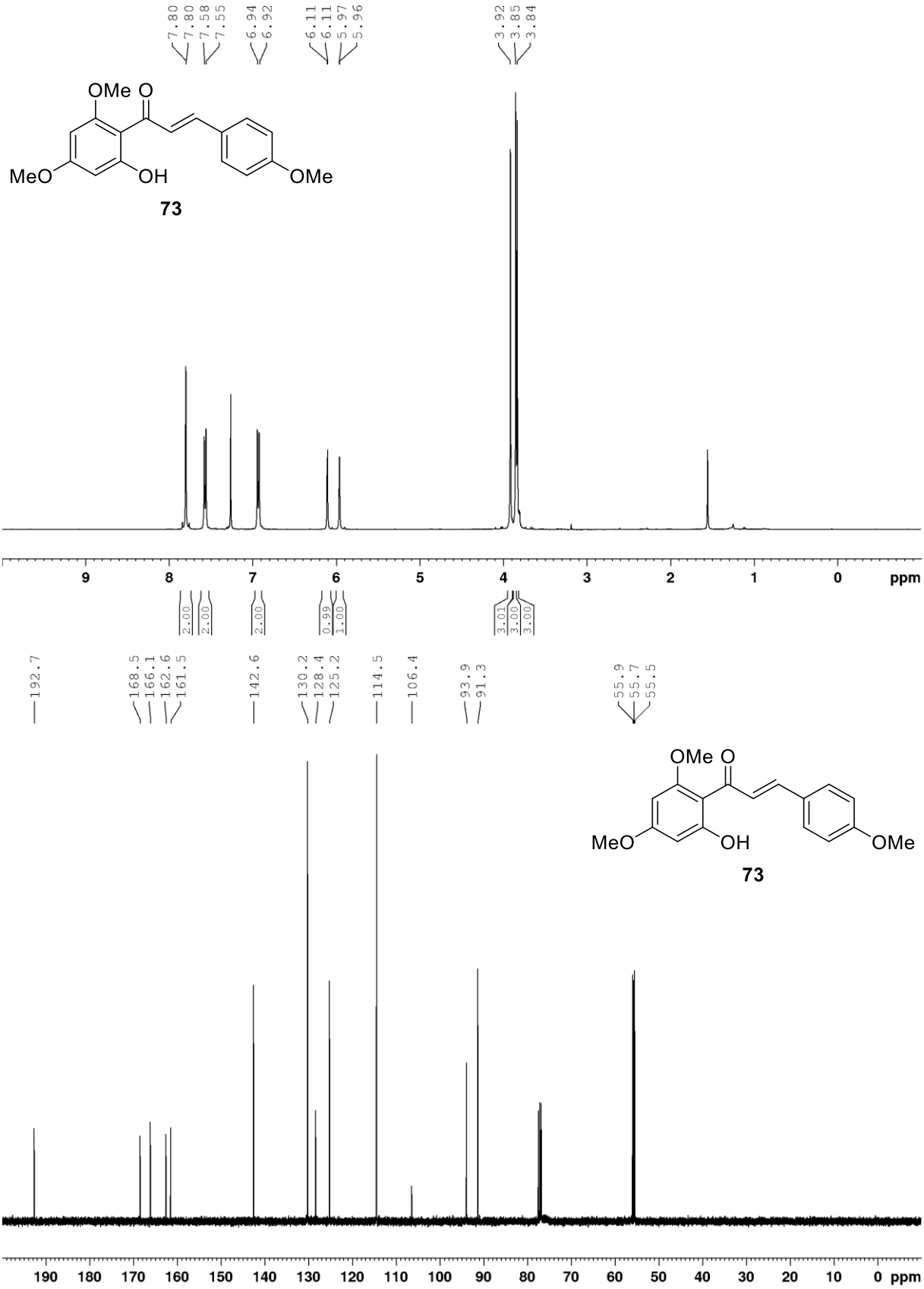
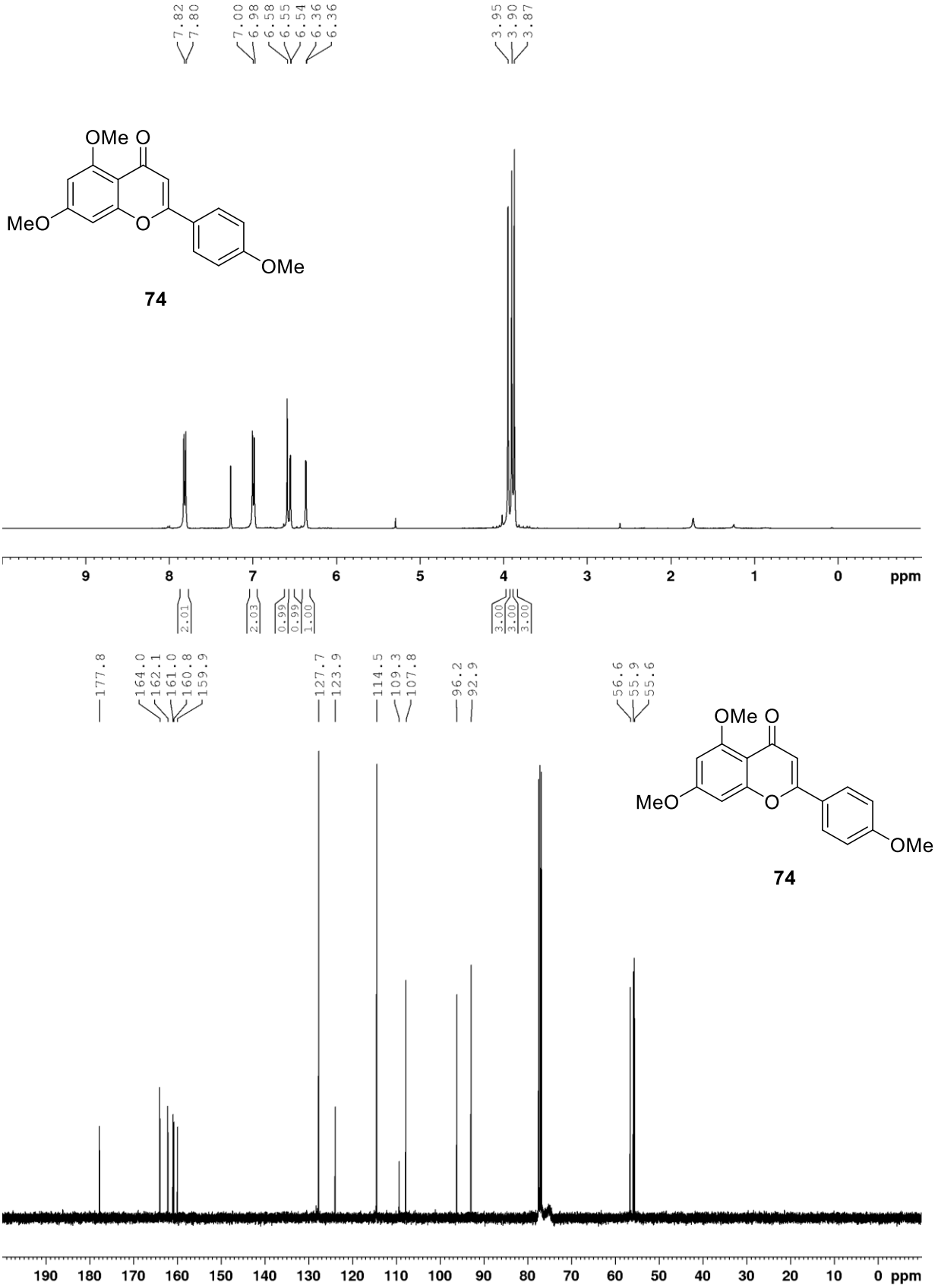
Appendix

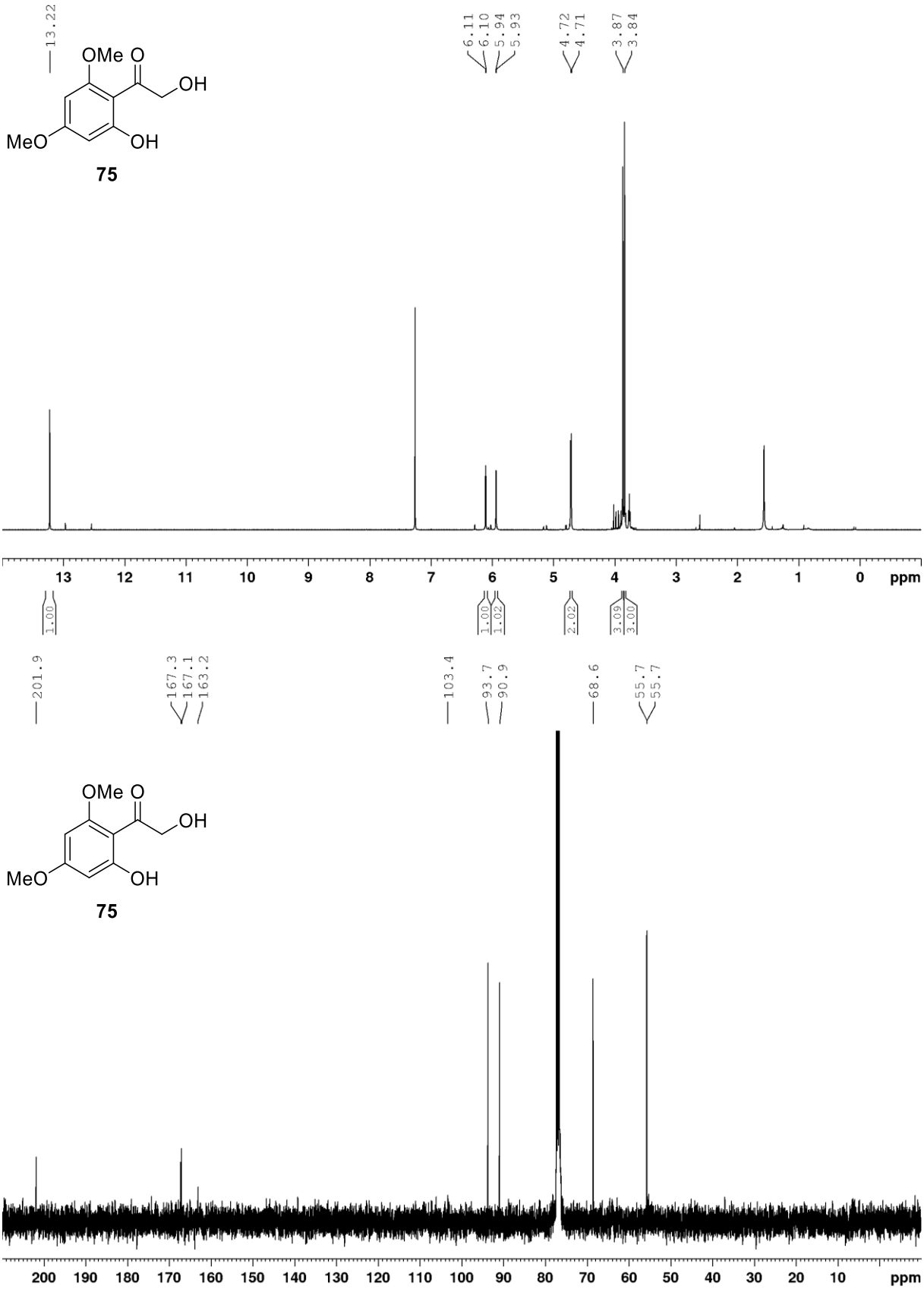
(*E*)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (73)



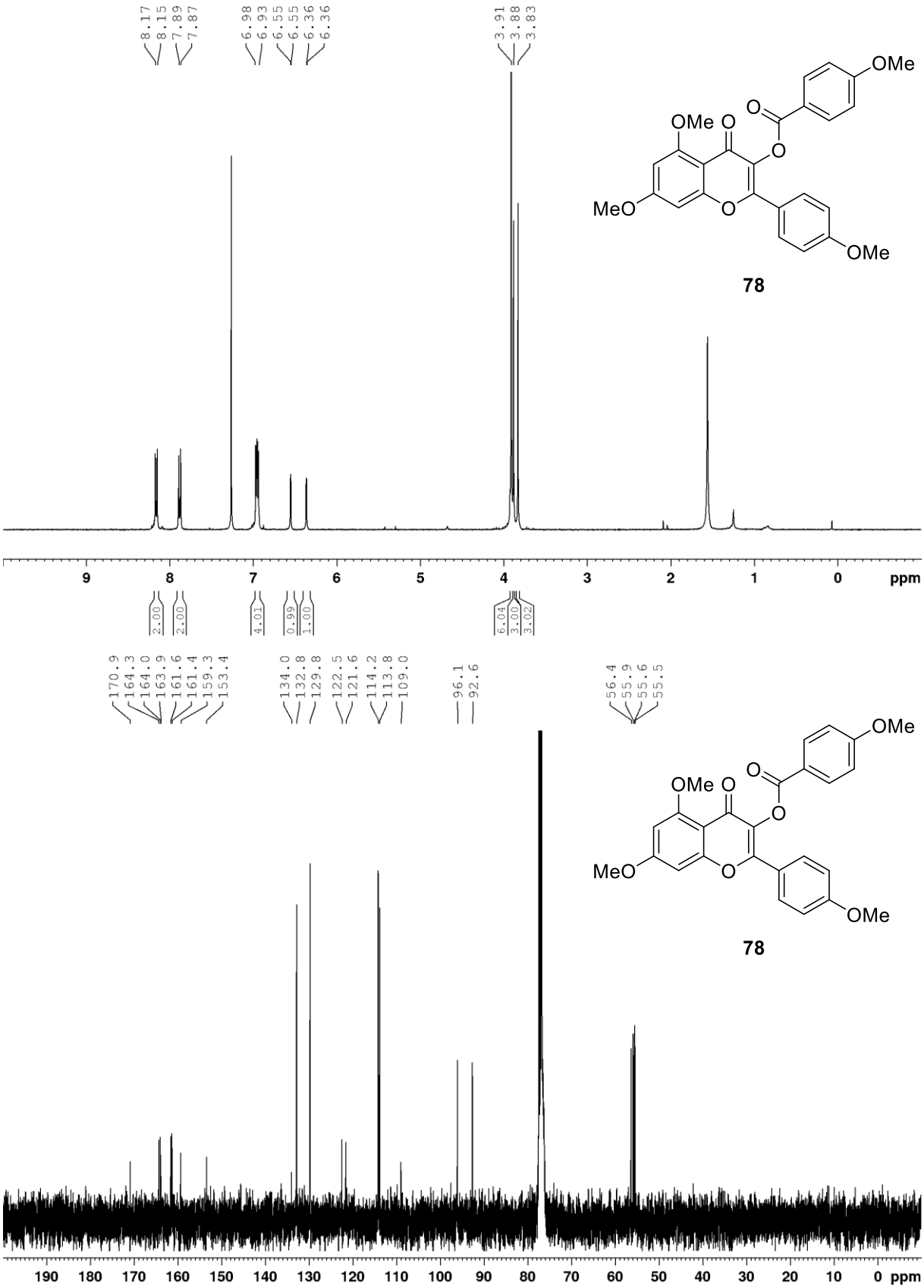
5,7-Dimethoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (74)



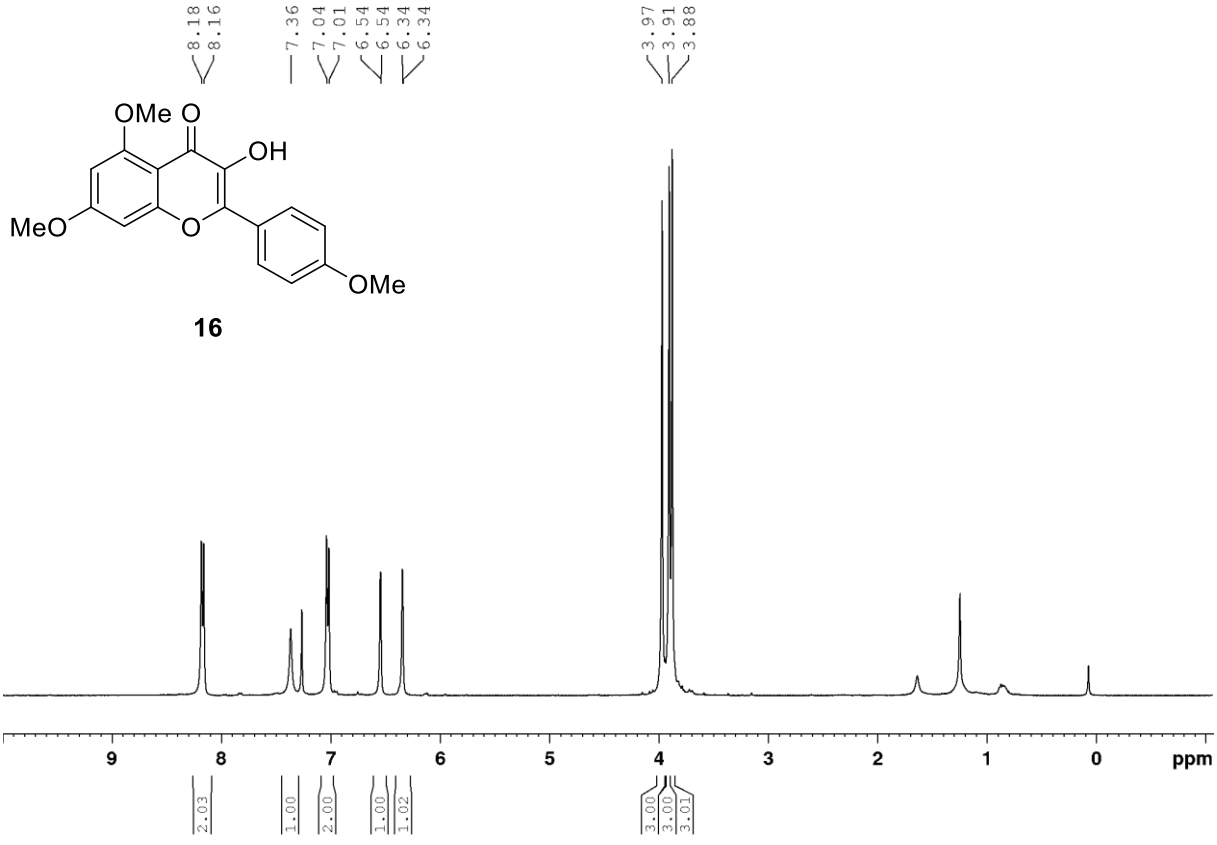
2-Hydroxy-1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (75)

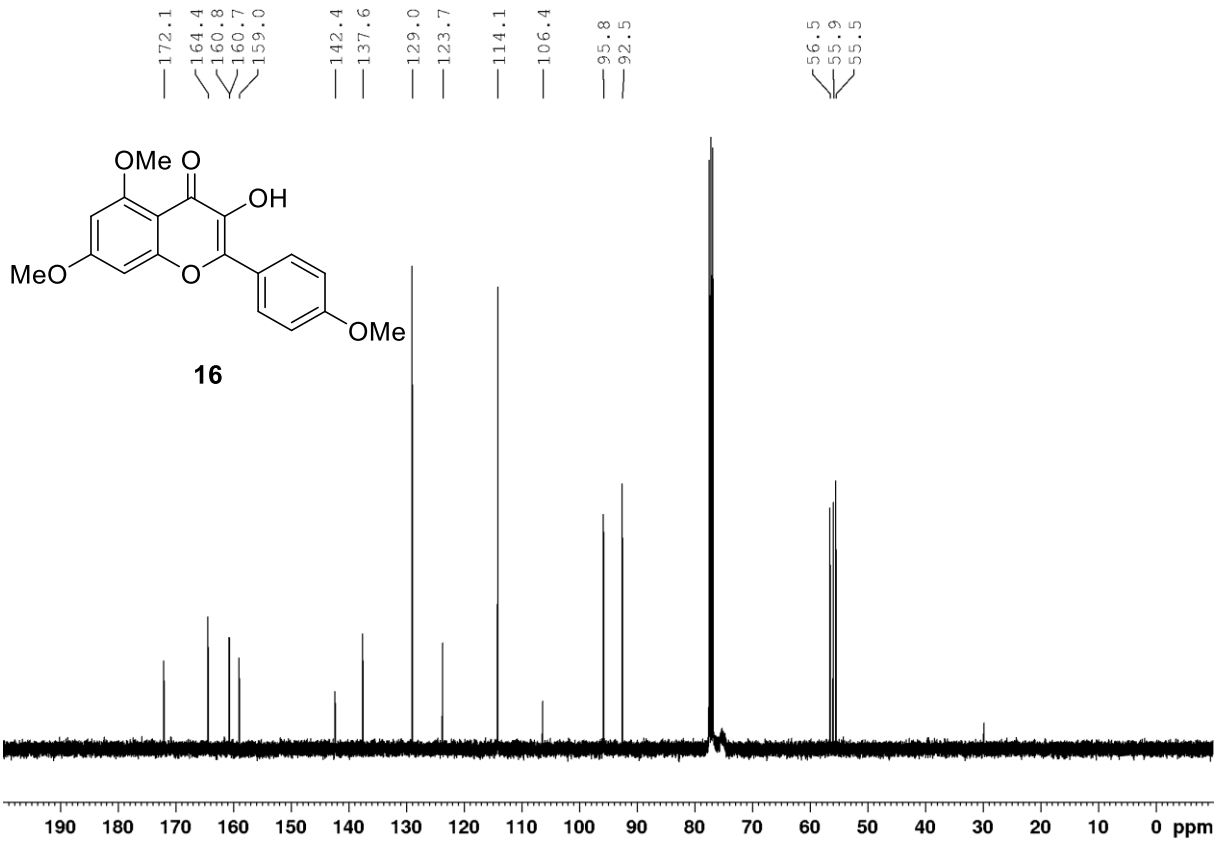


5,7-Dimethoxy-2-(4-methoxyphenyl)-4-oxo-4*H*-chromen-3-yl 4-methoxybenzoate (78)

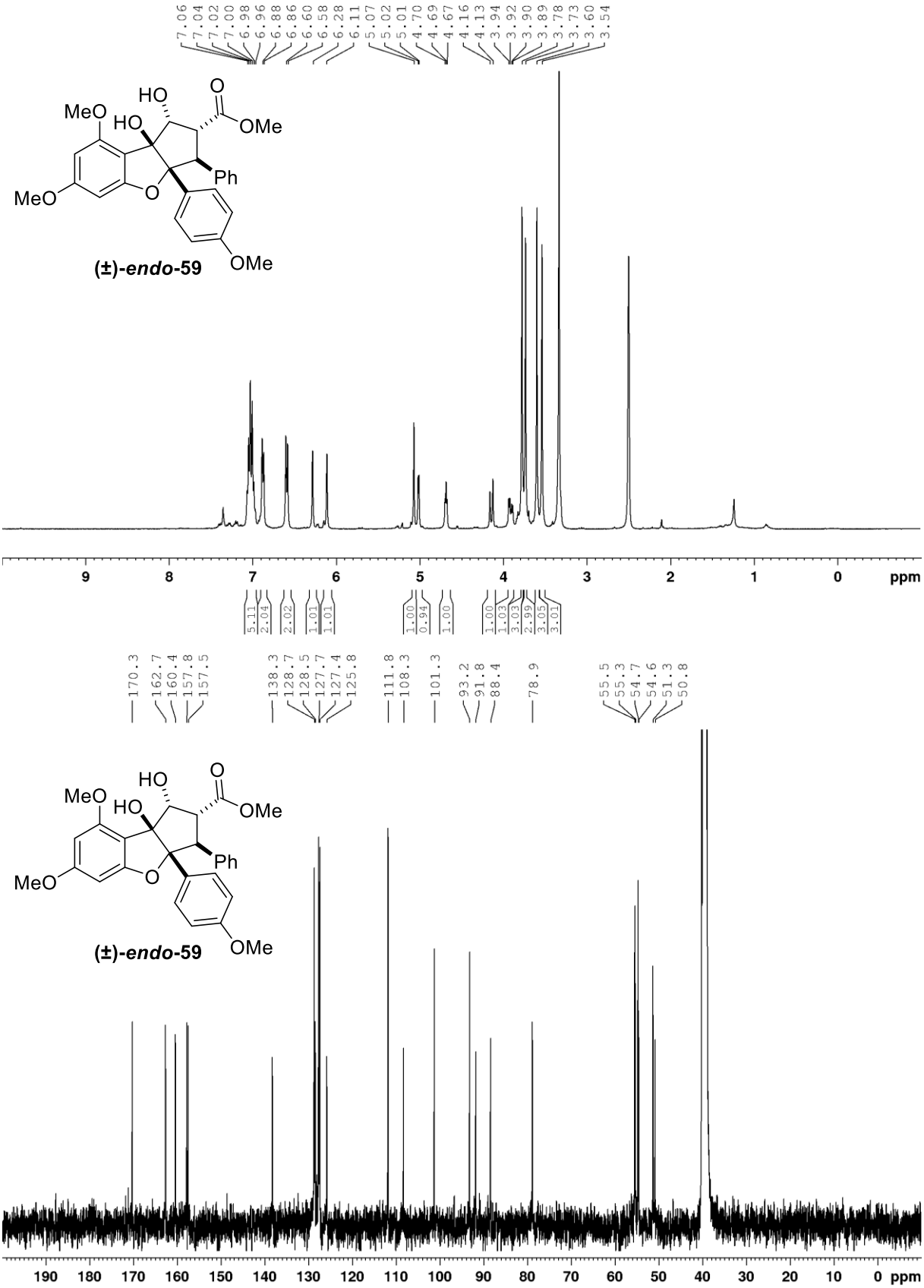


3-Hydroxy-5,7-dimethoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (16)

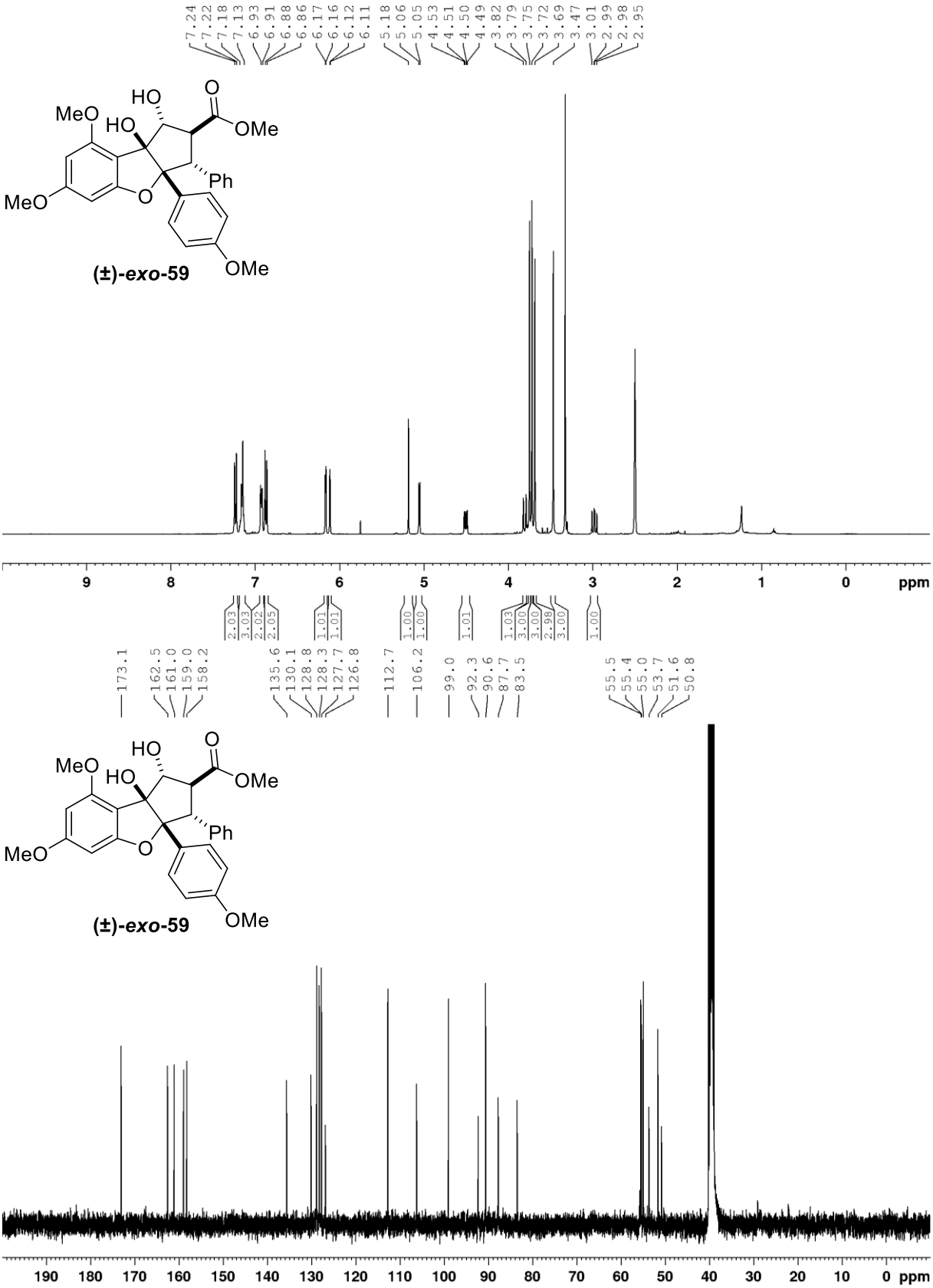




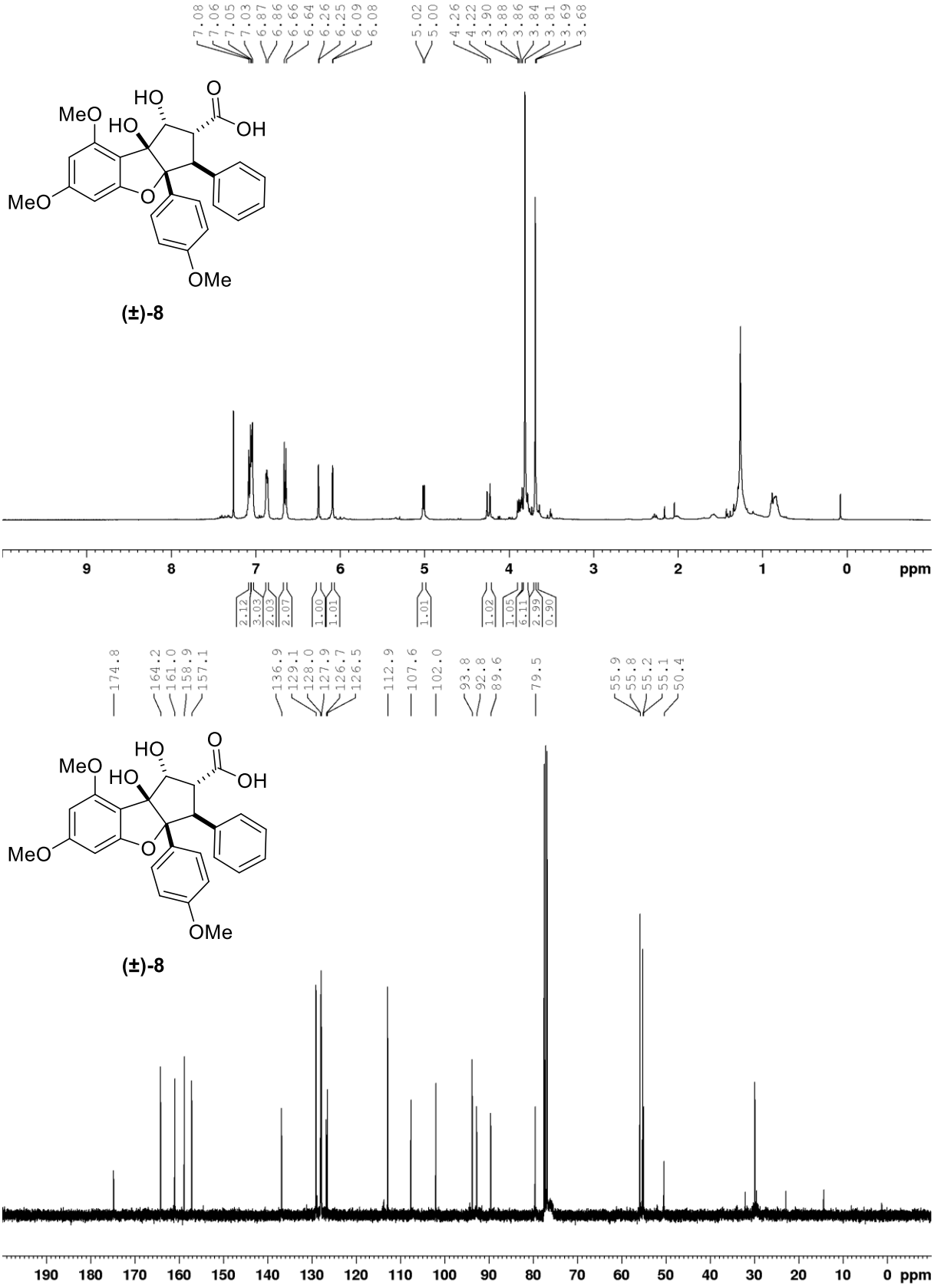
(±)-Methyl (1R,2R,3S,3aR,8bS)-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-*endo*-59)



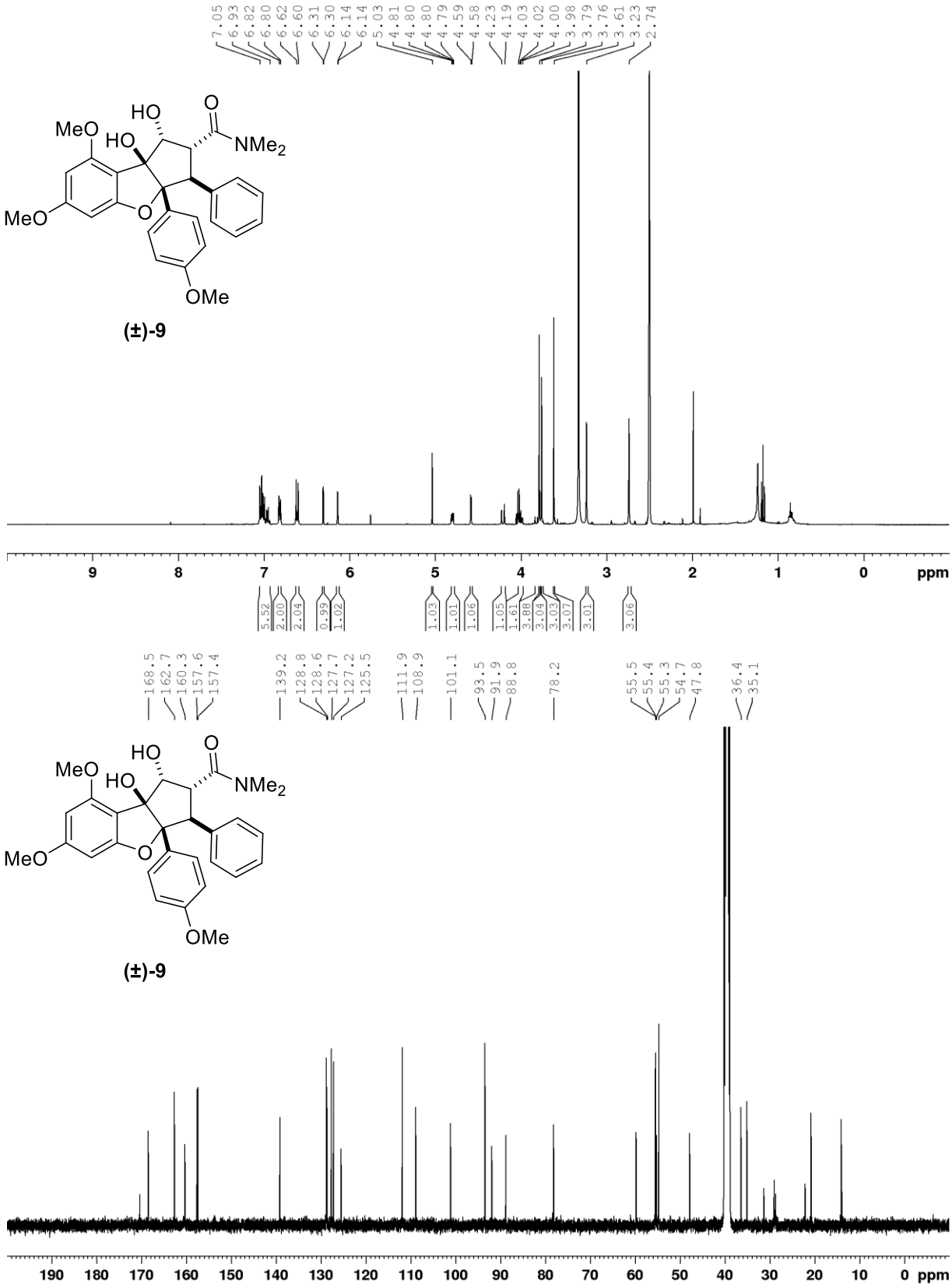
(±)-Methyl (1*R*,2*S*,3*R*,3a*R*,8b*S*)-1,8b-dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-*exo*-59)



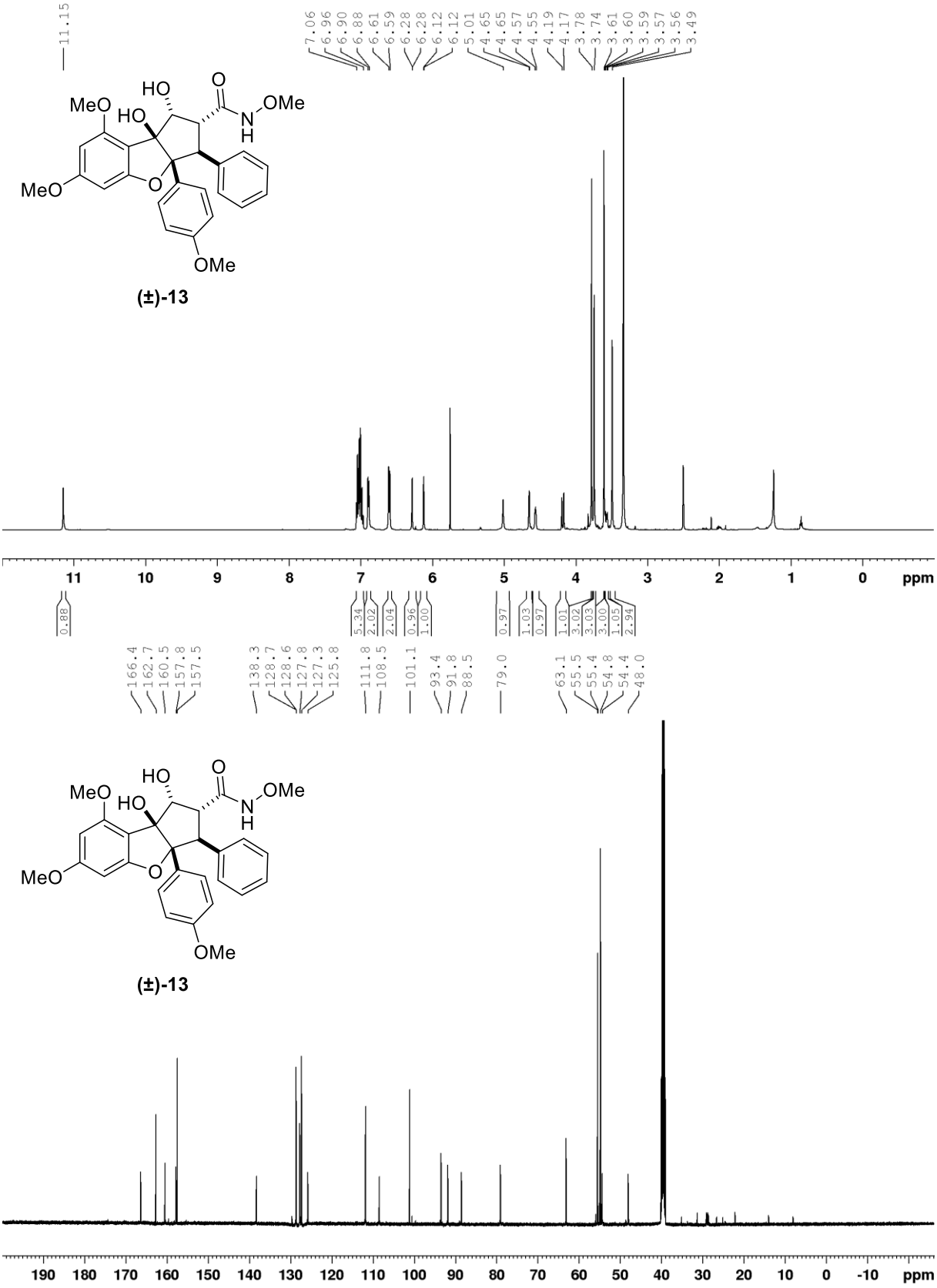
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid ((±)-8)



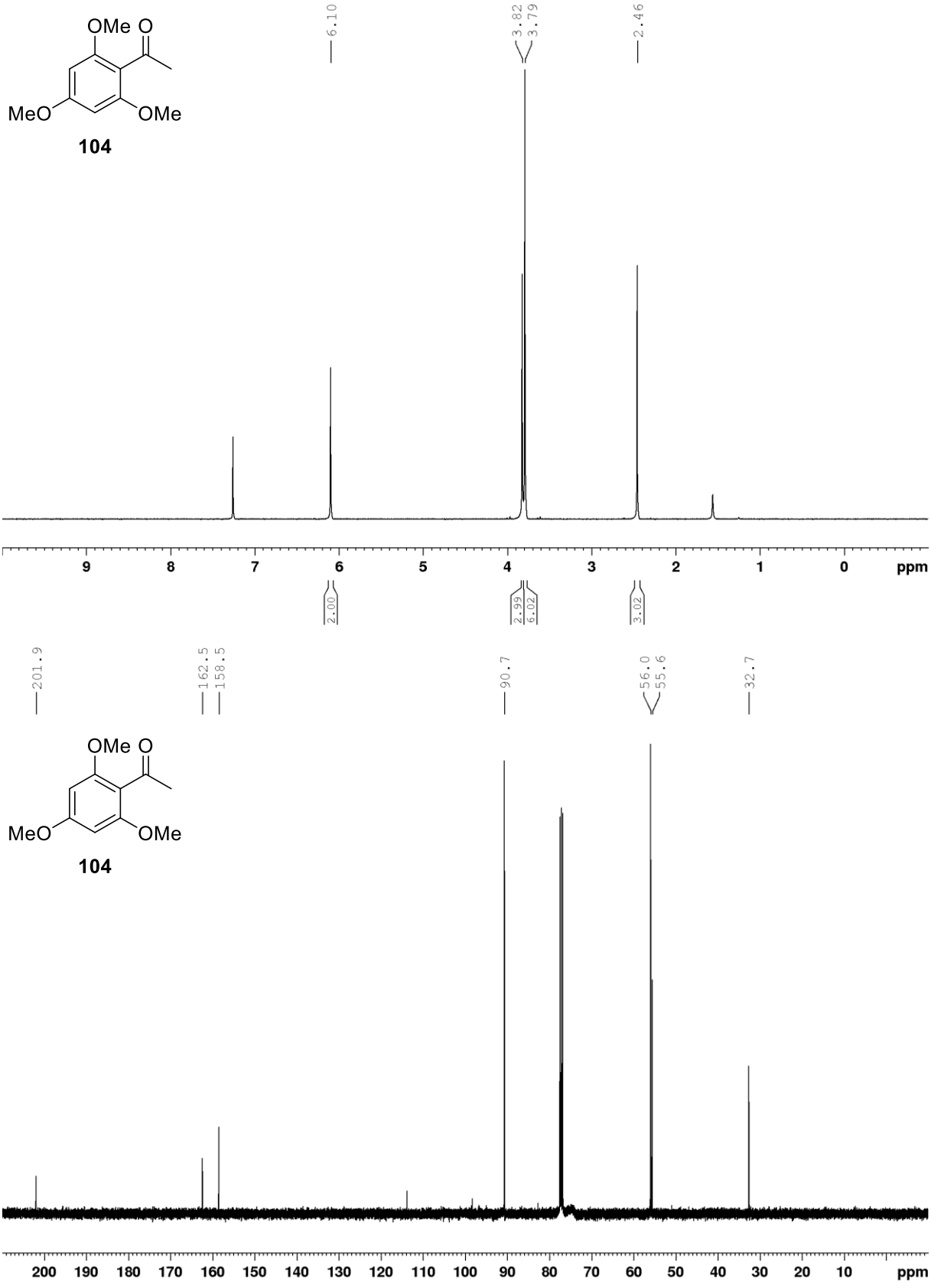
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-Rocaglamide, (±)-9)



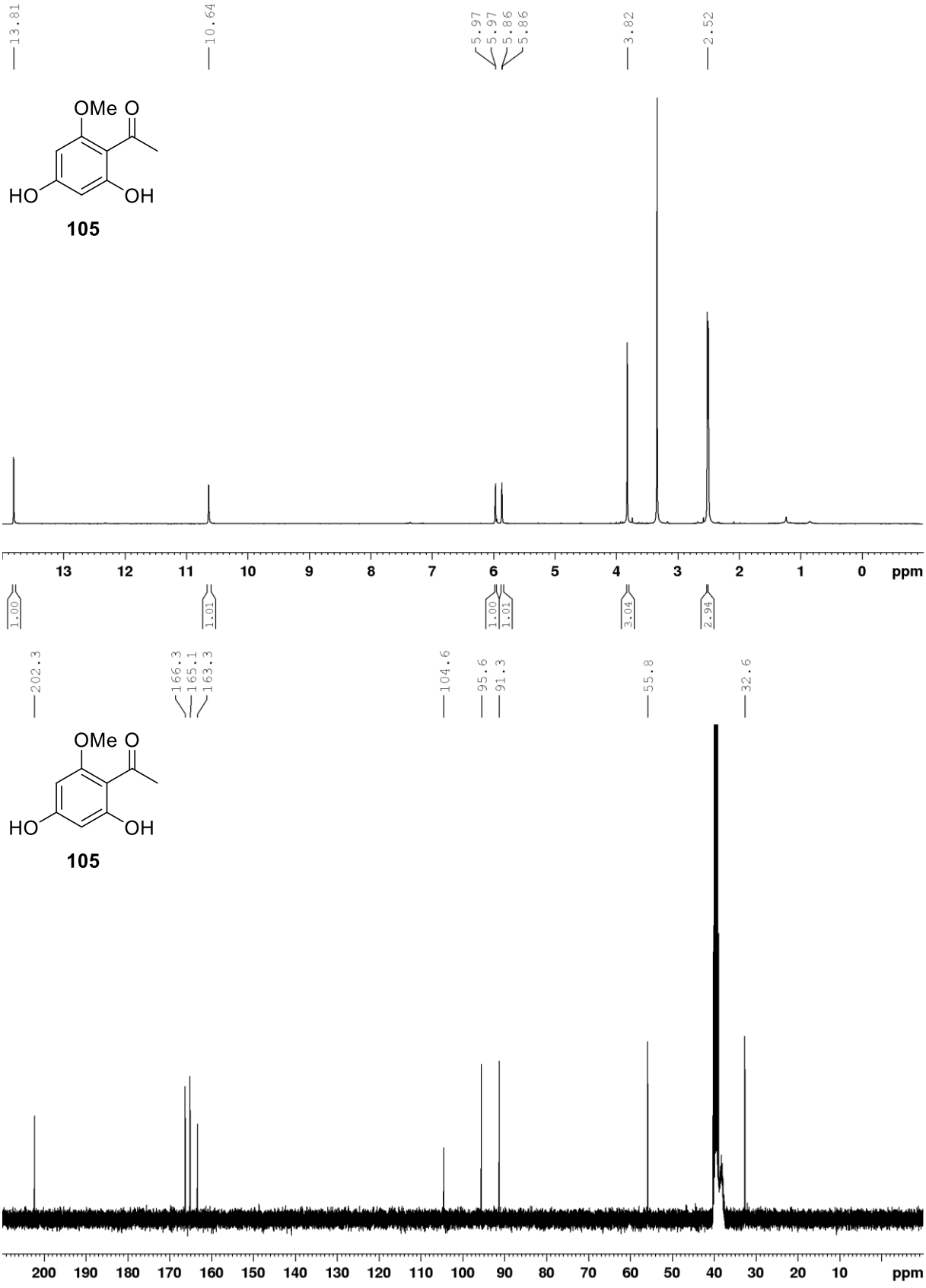
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-*N*,6,8-trimethoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-CR-31-B, (±)-13)



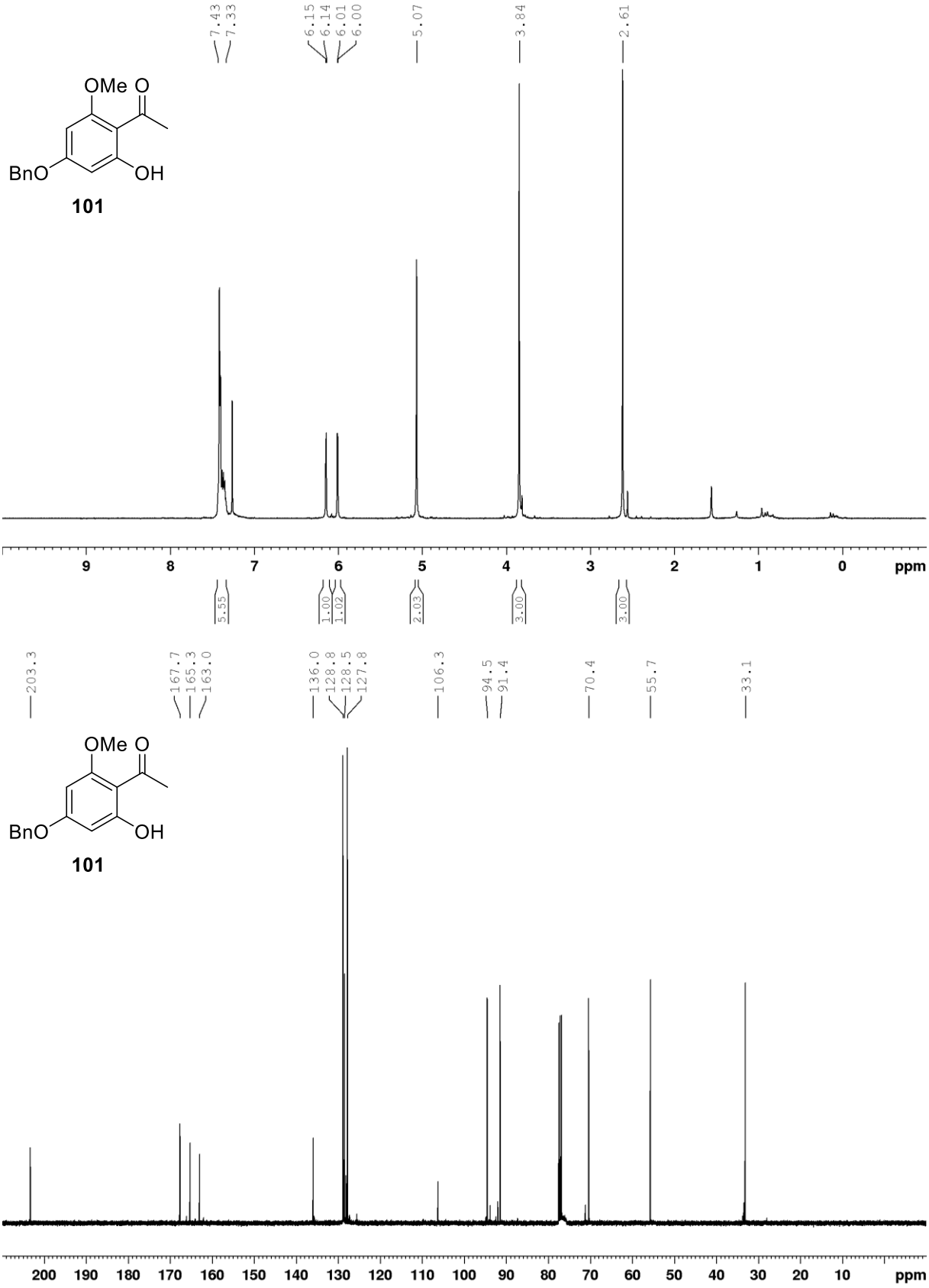
1-(2,4,6-Trimethoxyphenyl)ethan-1-one (104)



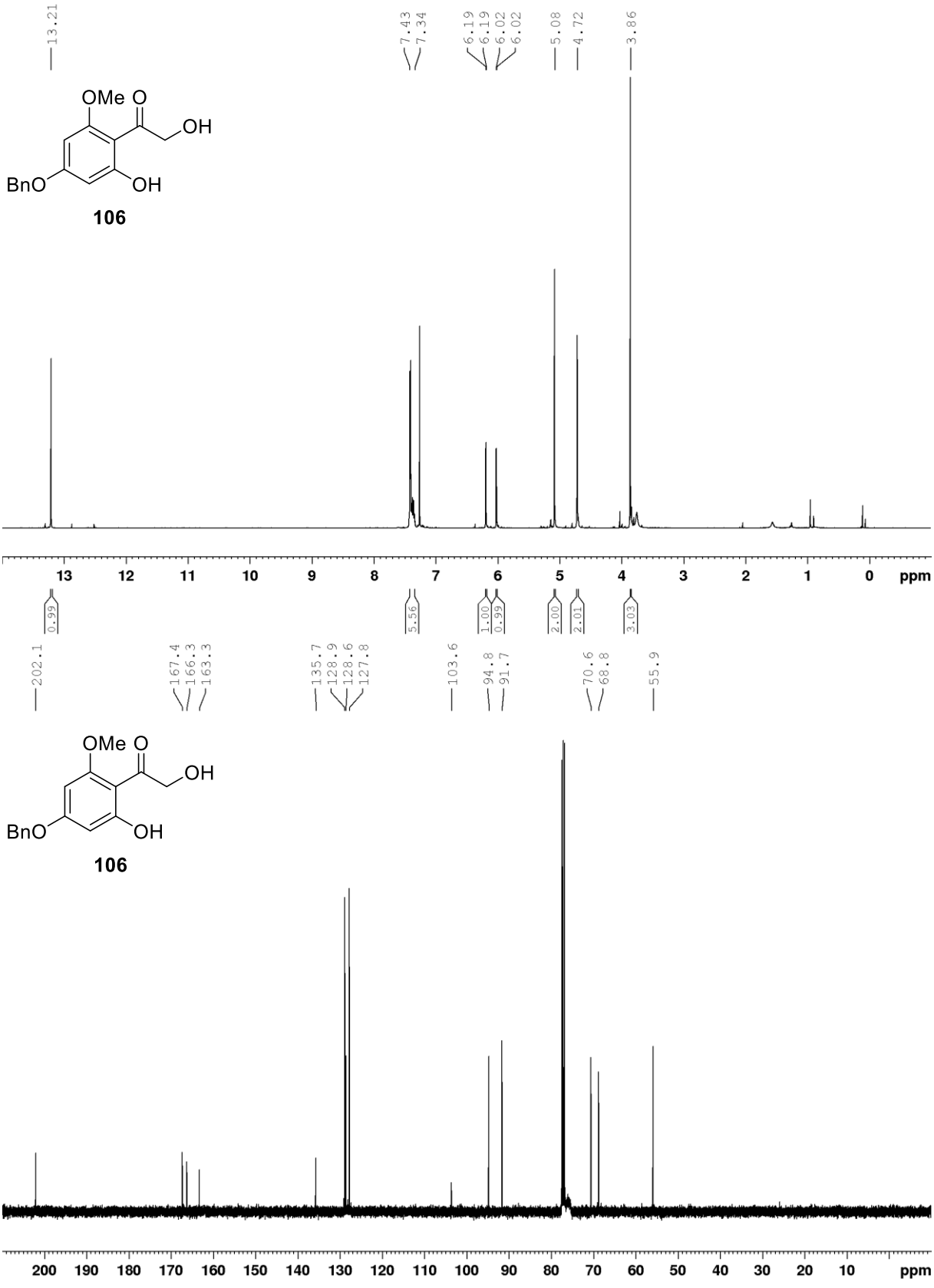
1-(2,4-Dihydroxy-6-methoxyphenyl)ethan-1-one (105)



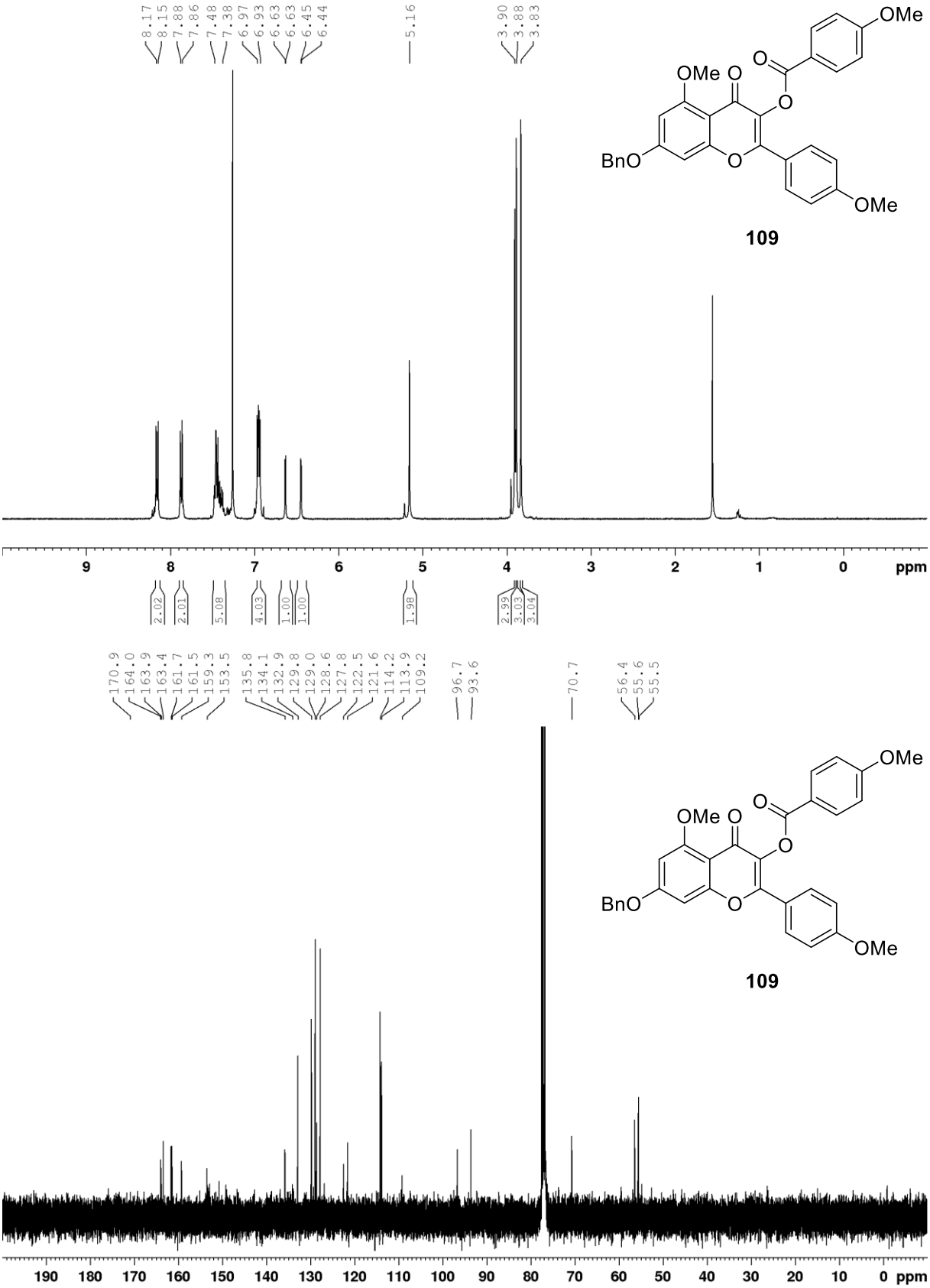
1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)ethan-1-one (101)



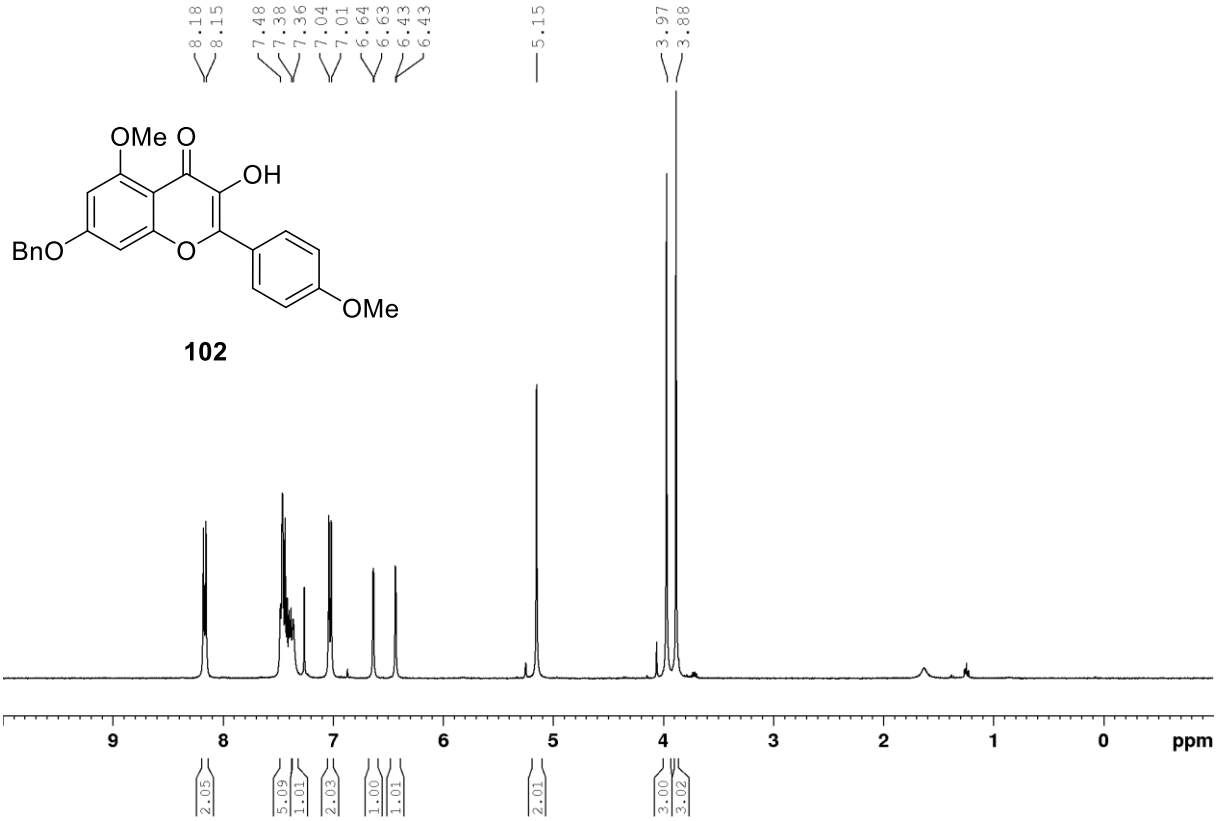
1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)-2-hydroxyethan-1-one (106)

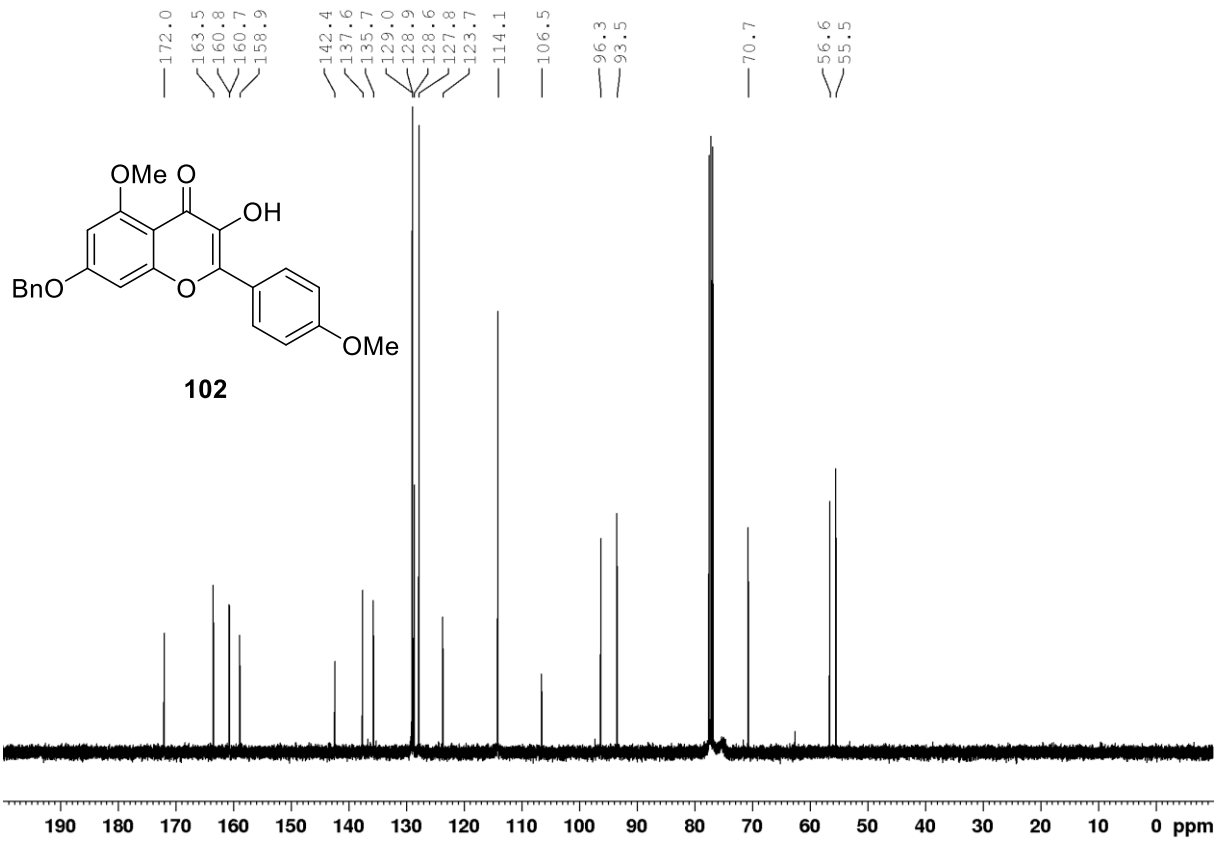


7-(Benzyloxy)-5-methoxy-2-(4-methoxyphenyl)-4-oxo-4*H*-chromen-3-yl 4-methoxybenzo-ate (109)

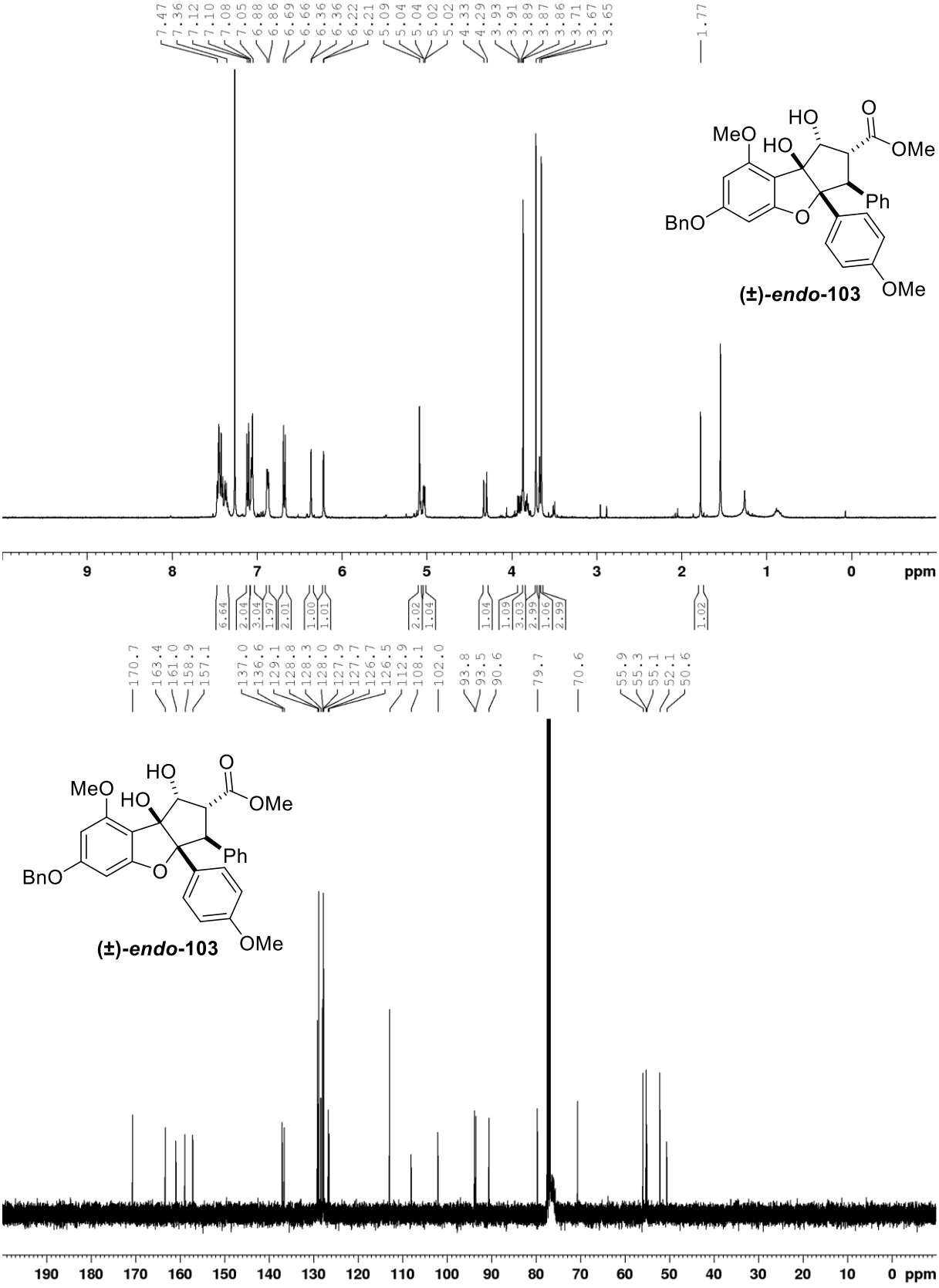


7-(Benzyloxy)-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (105)

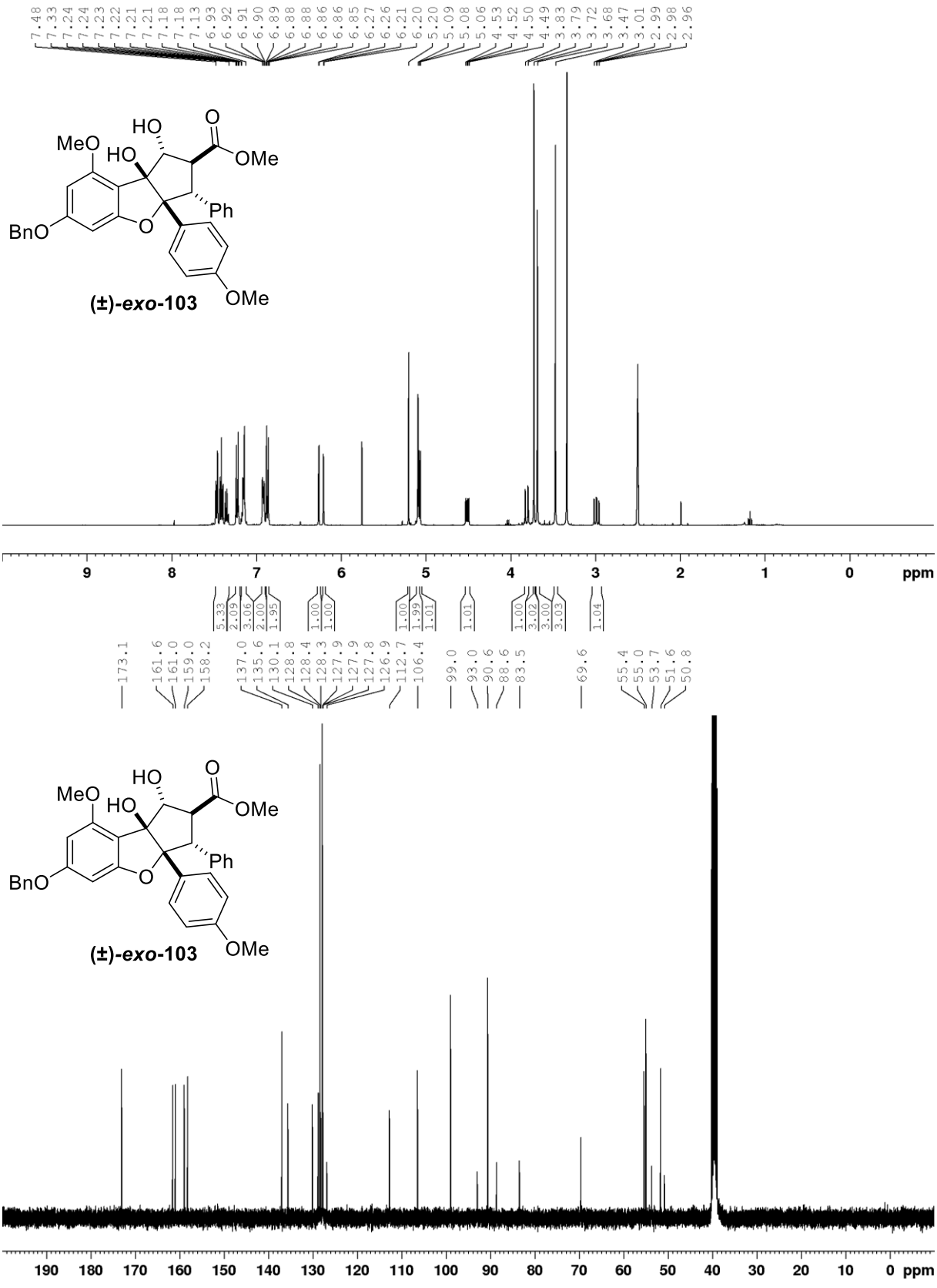




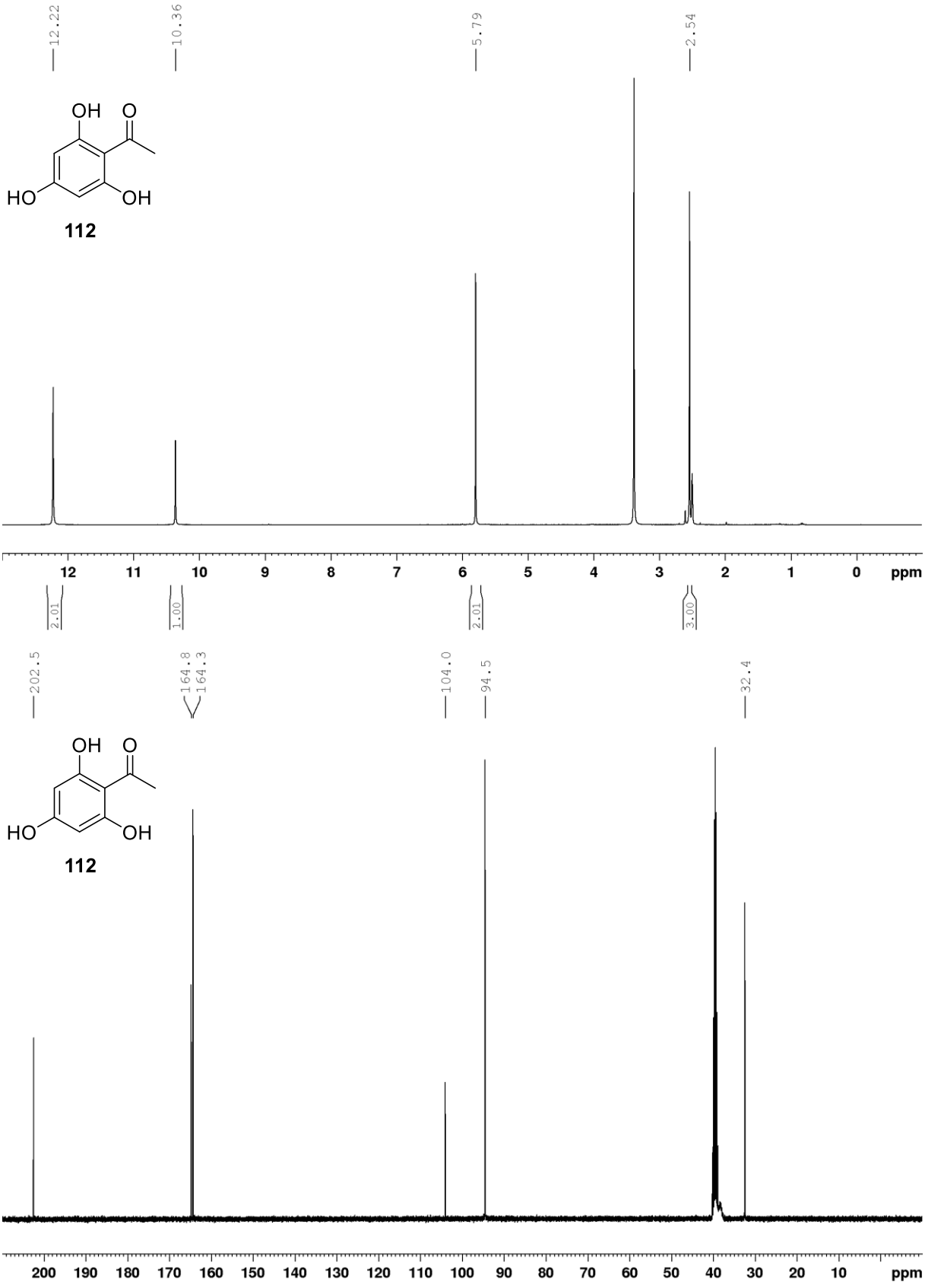
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-*endo*-103)



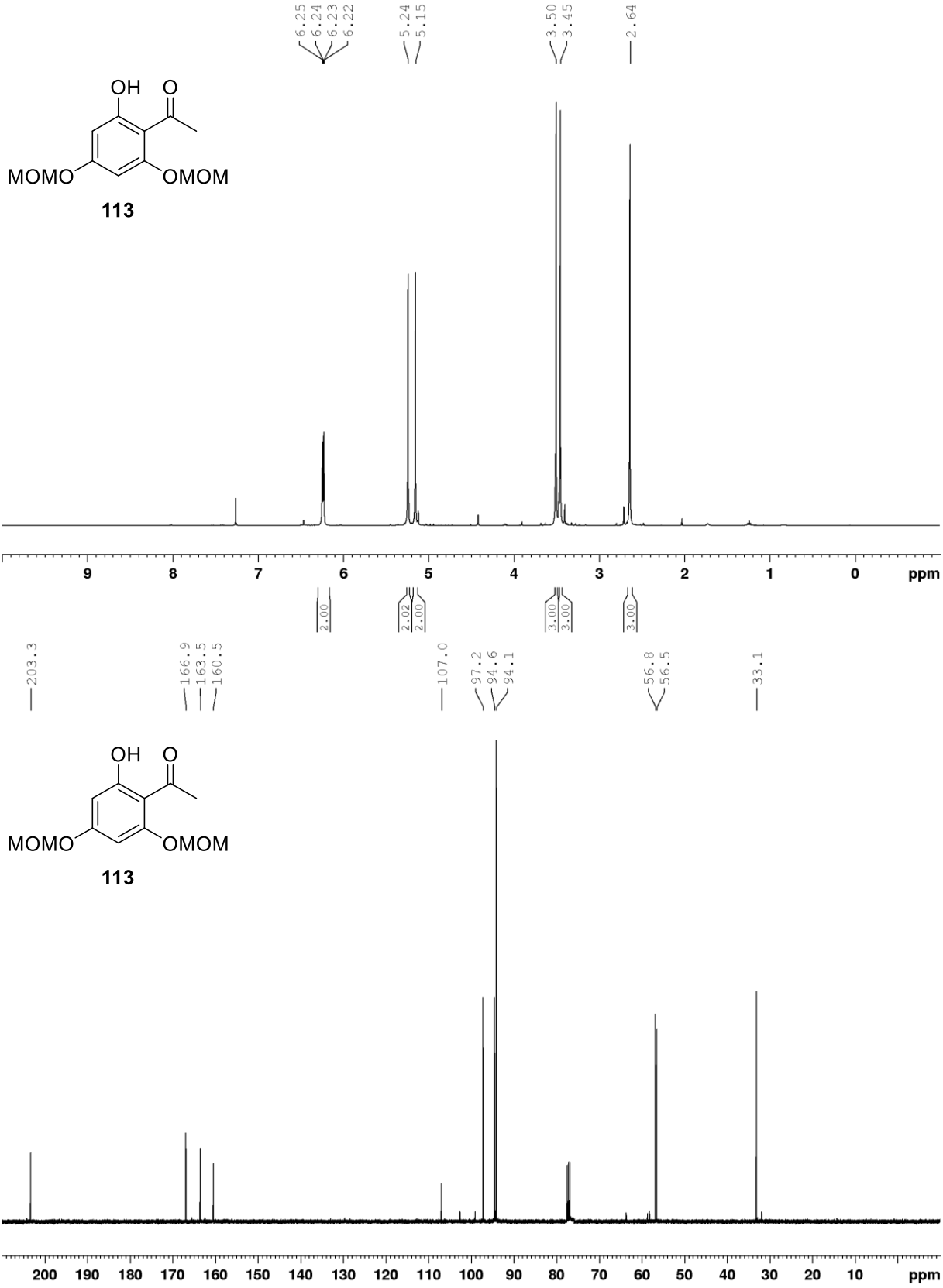
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-*exo*-103)



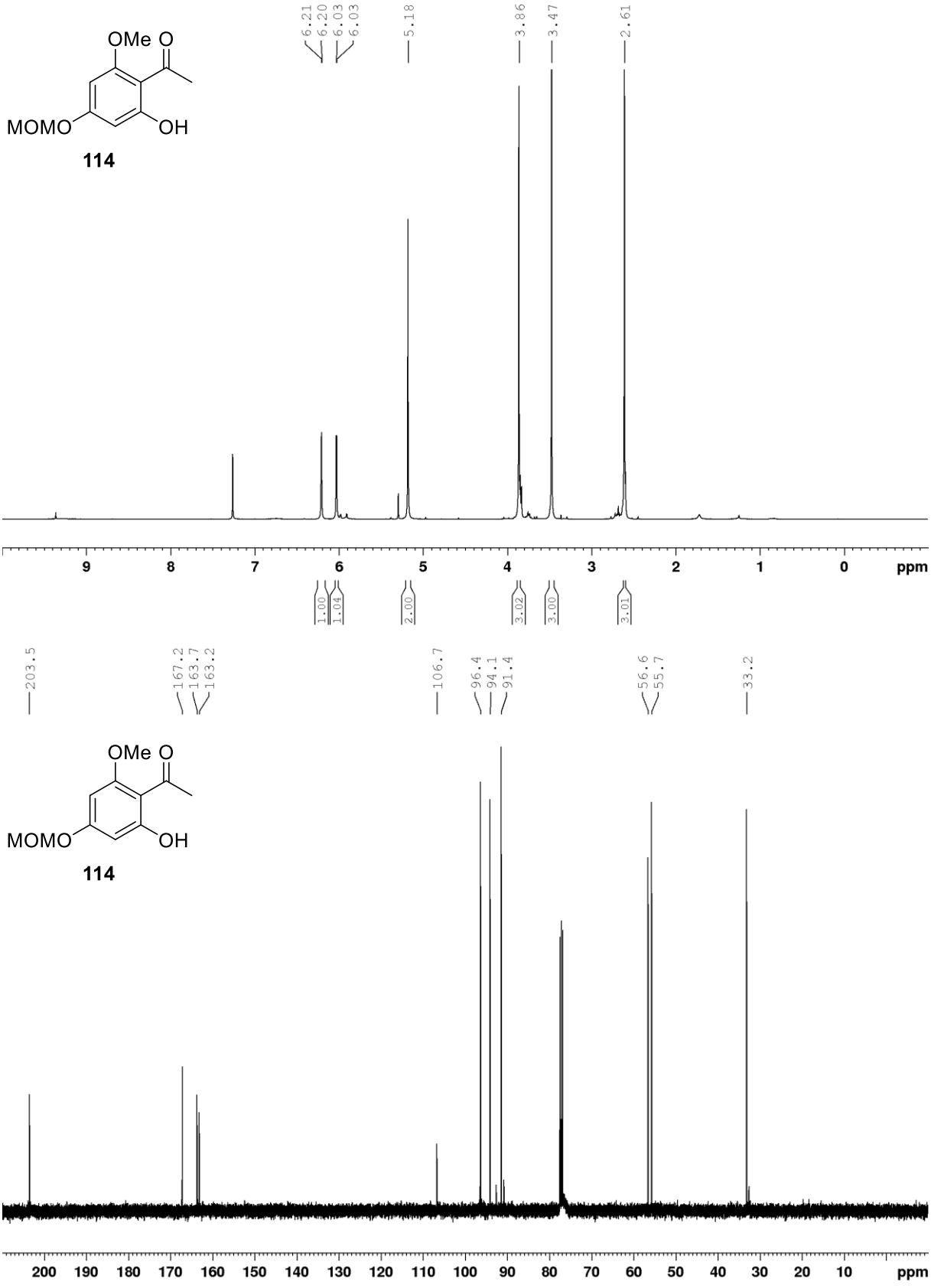
1-(2,4,6-Trihydroxyphenyl)ethan-1-one (112)



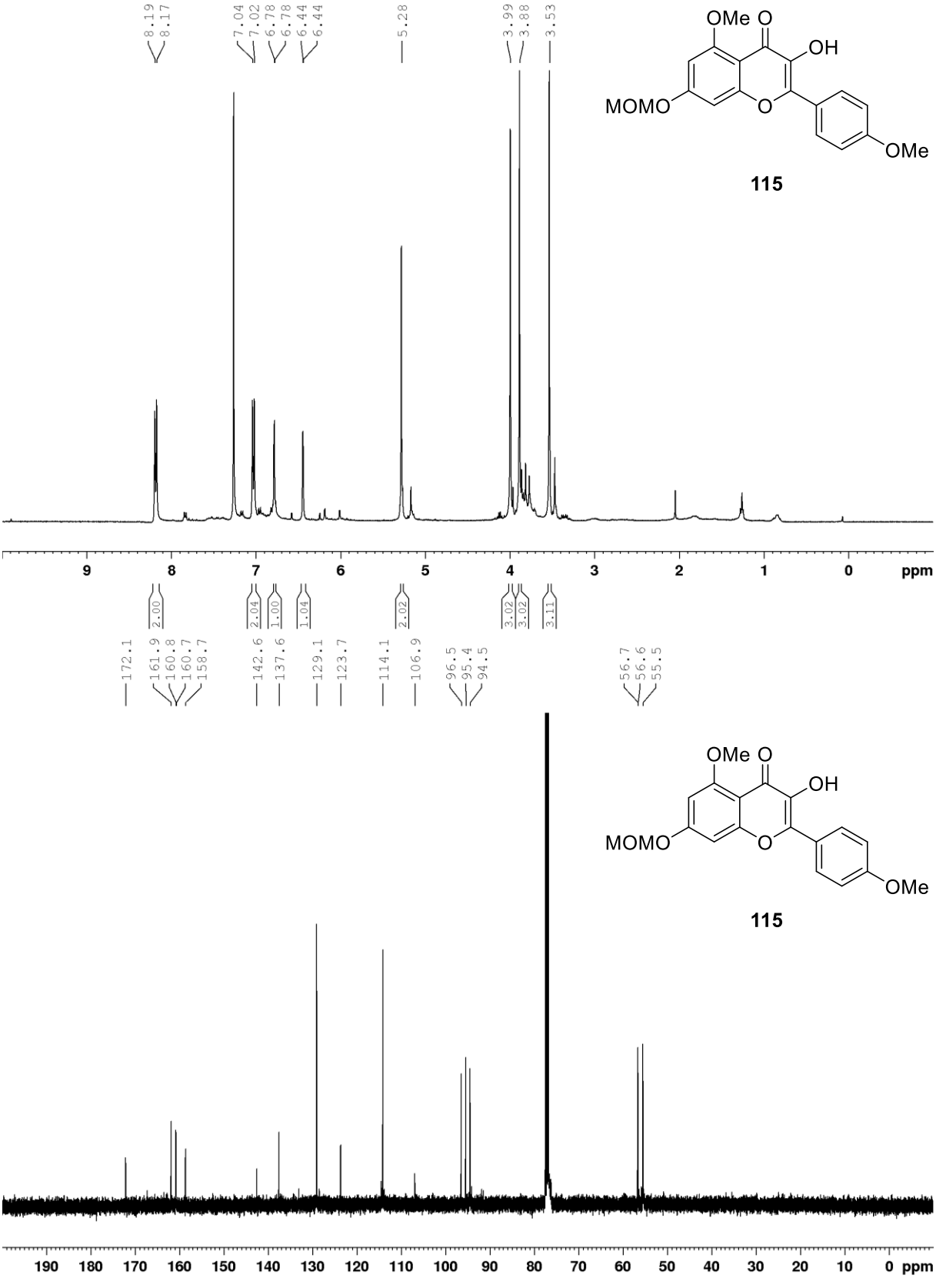
1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)ethan-1-one (113)



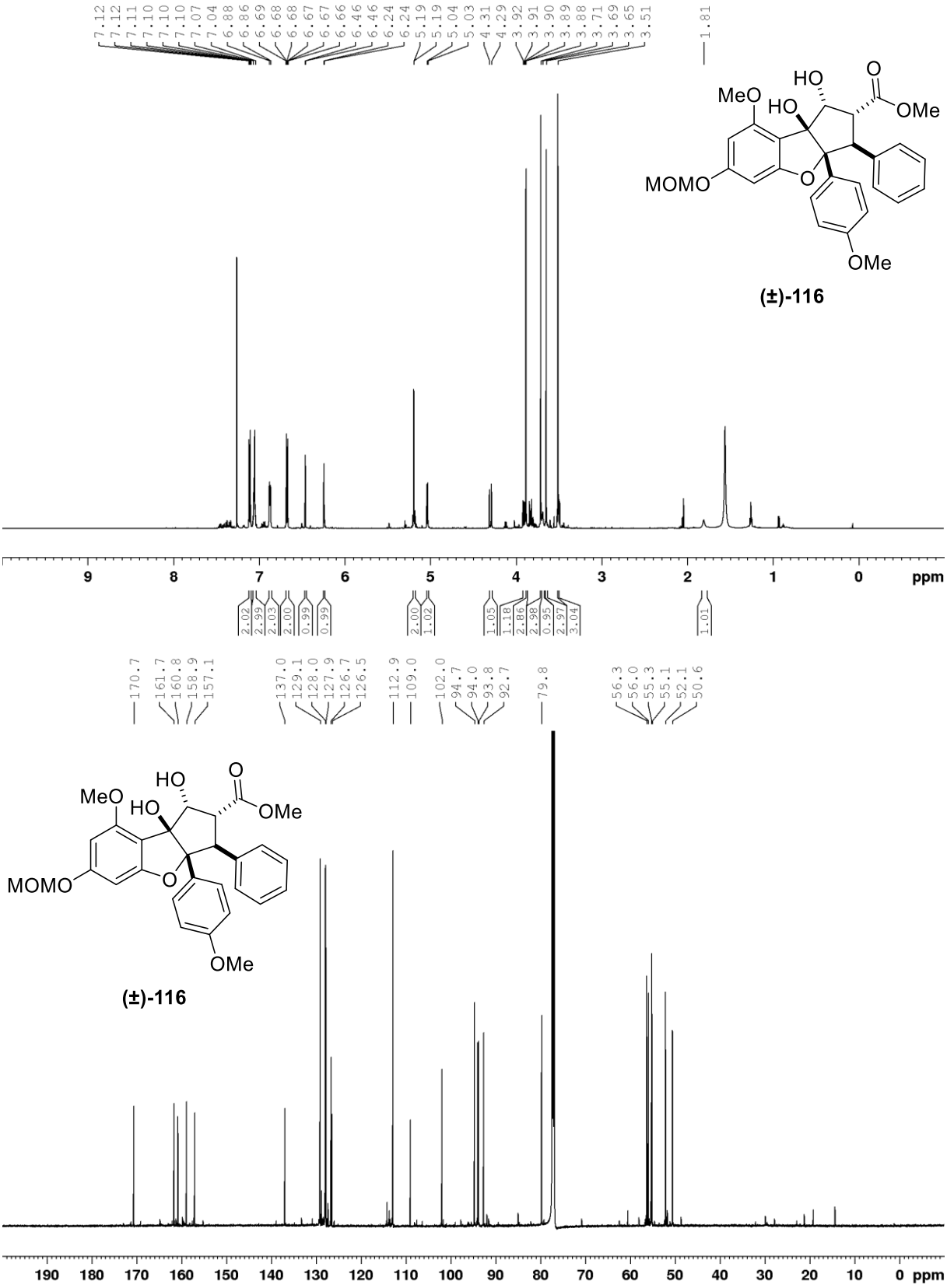
1-(2-Hydroxy-6-methoxy-4-(methoxymethoxy)phenyl)ethan-1-one (114)



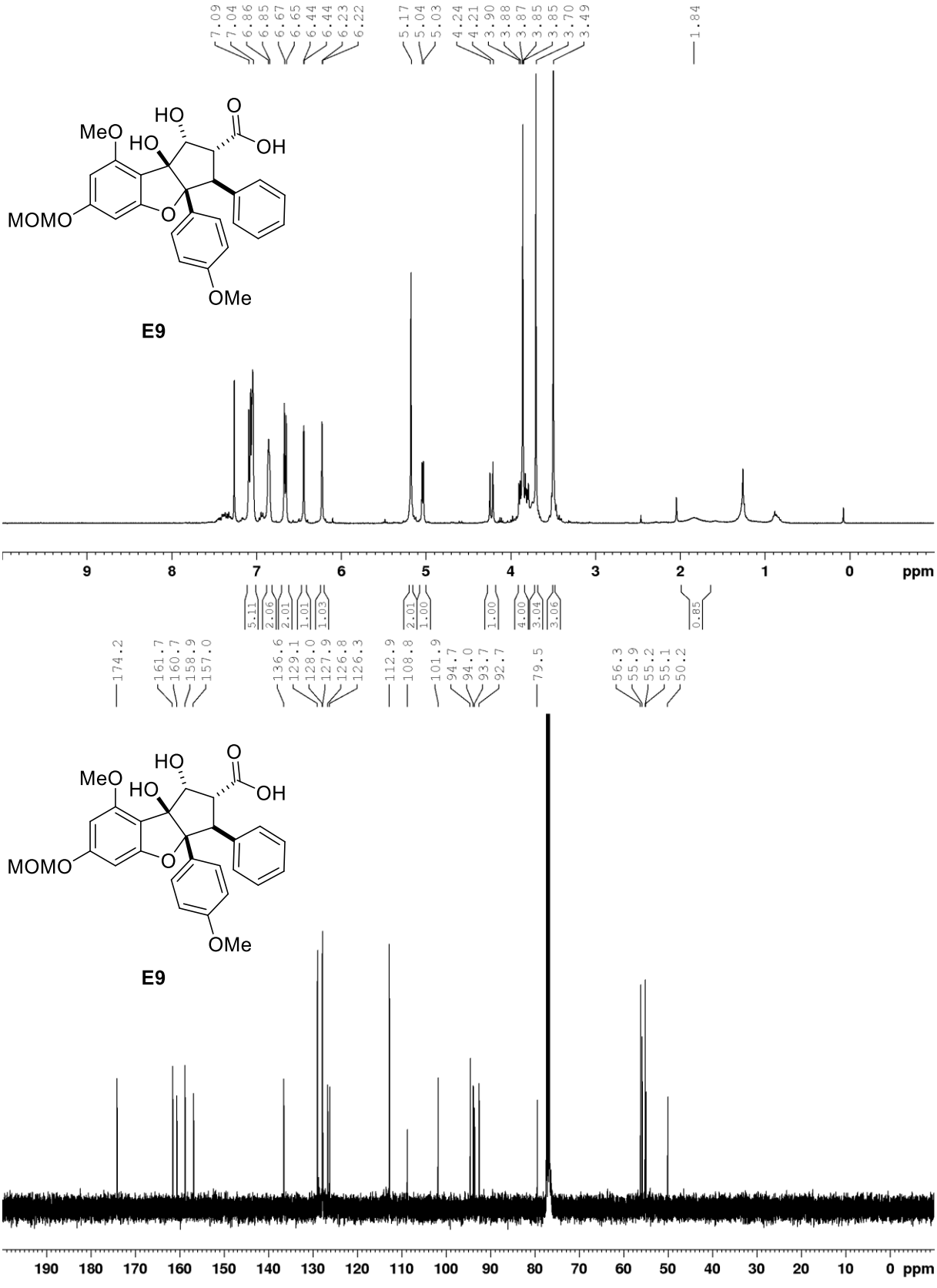
3-Hydroxy-5-methoxy-7-(methoxymethoxy)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (115)



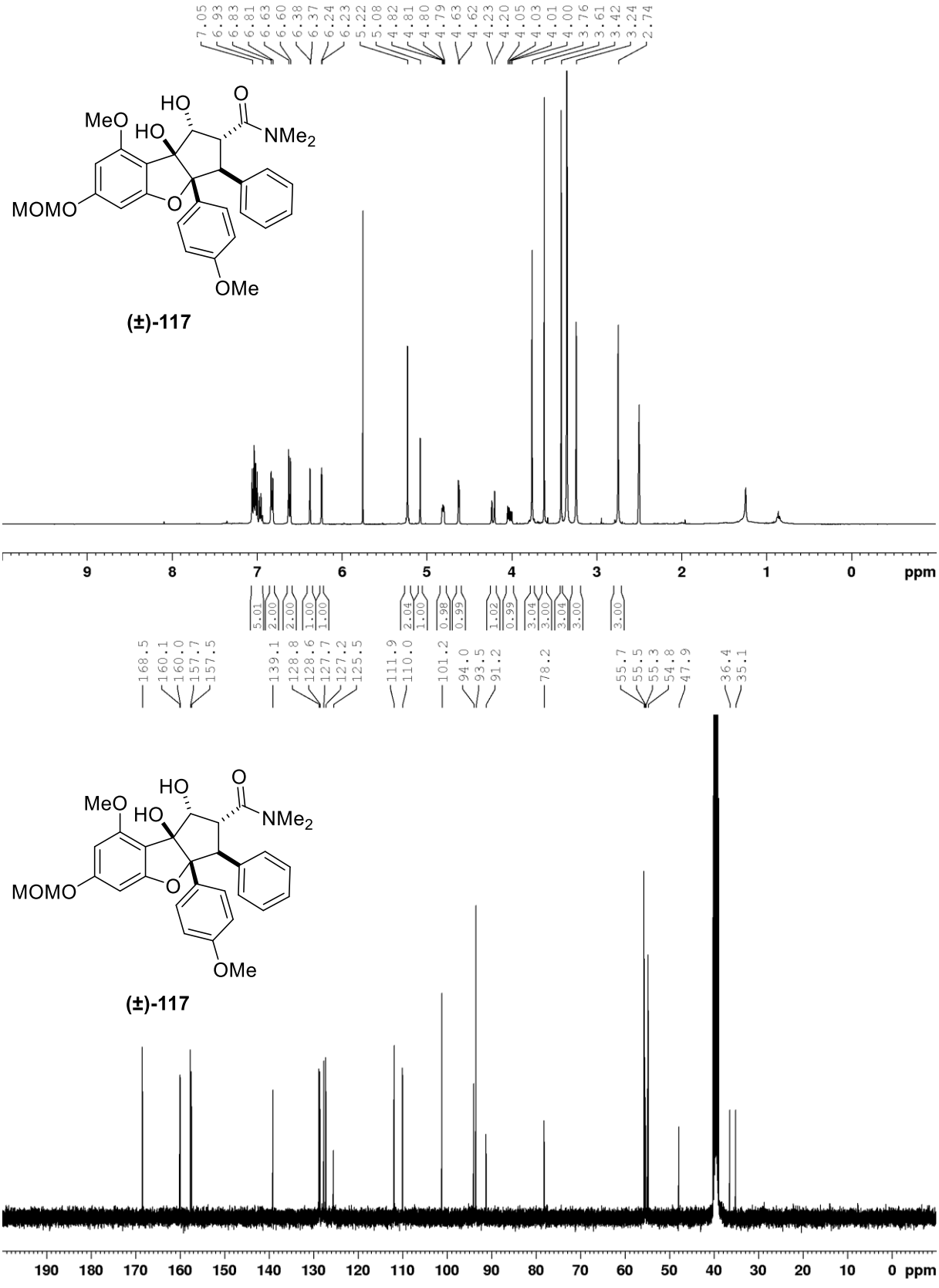
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-116)



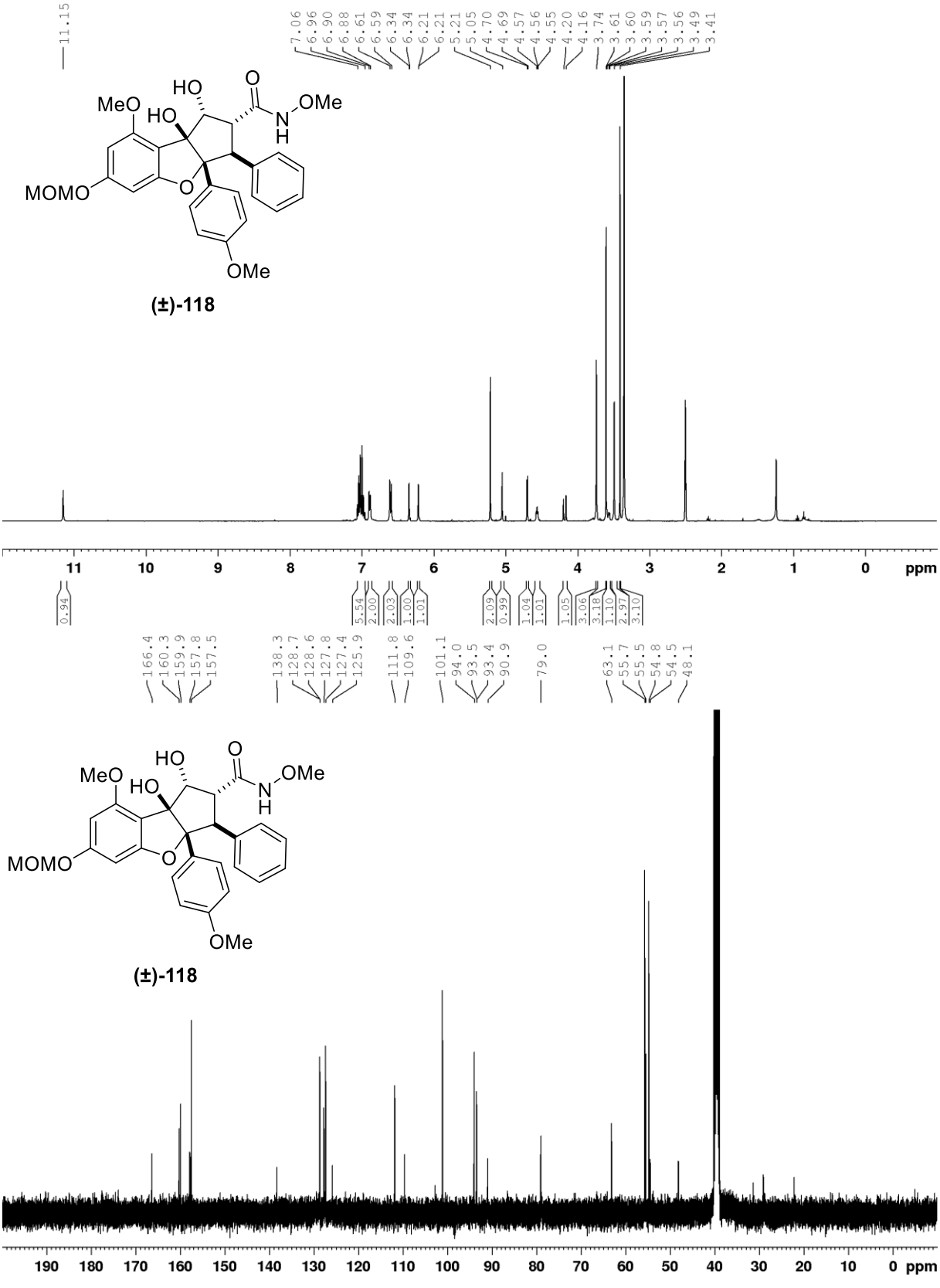
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (E9)



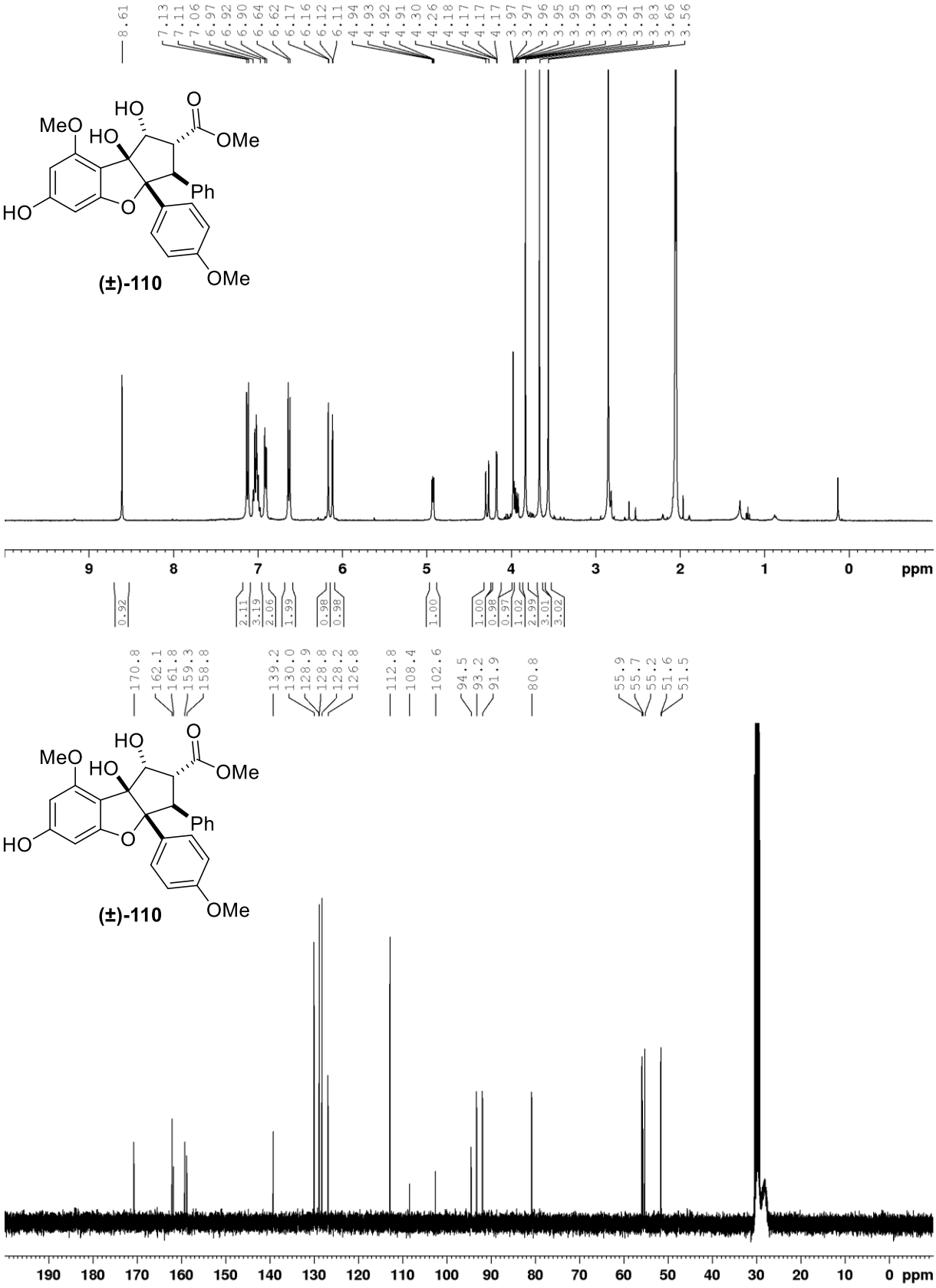
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-117)



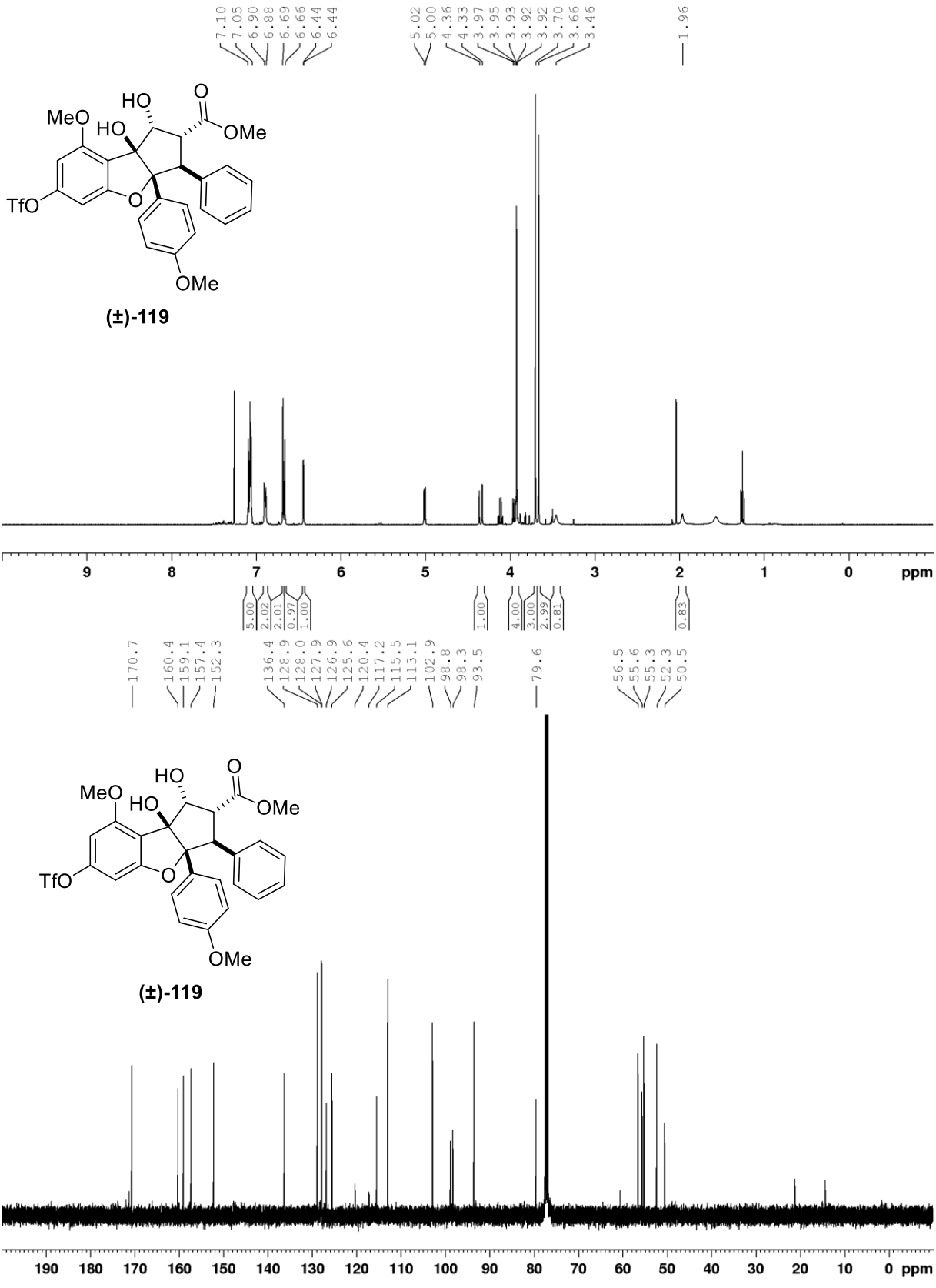
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-*N*,8-dimethoxy-6-(methoxymethoxy)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-118)



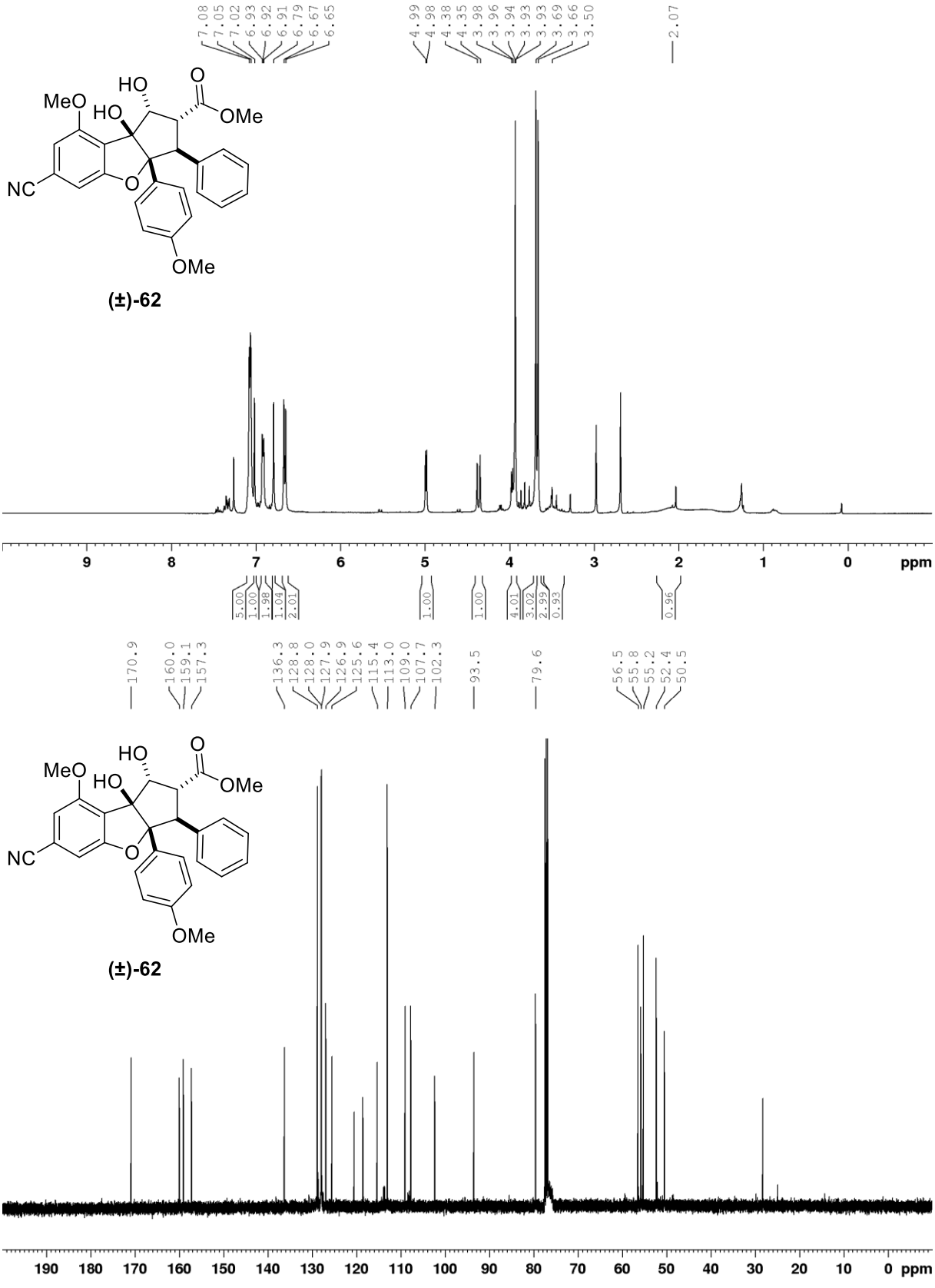
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,6,8b-trihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-110)



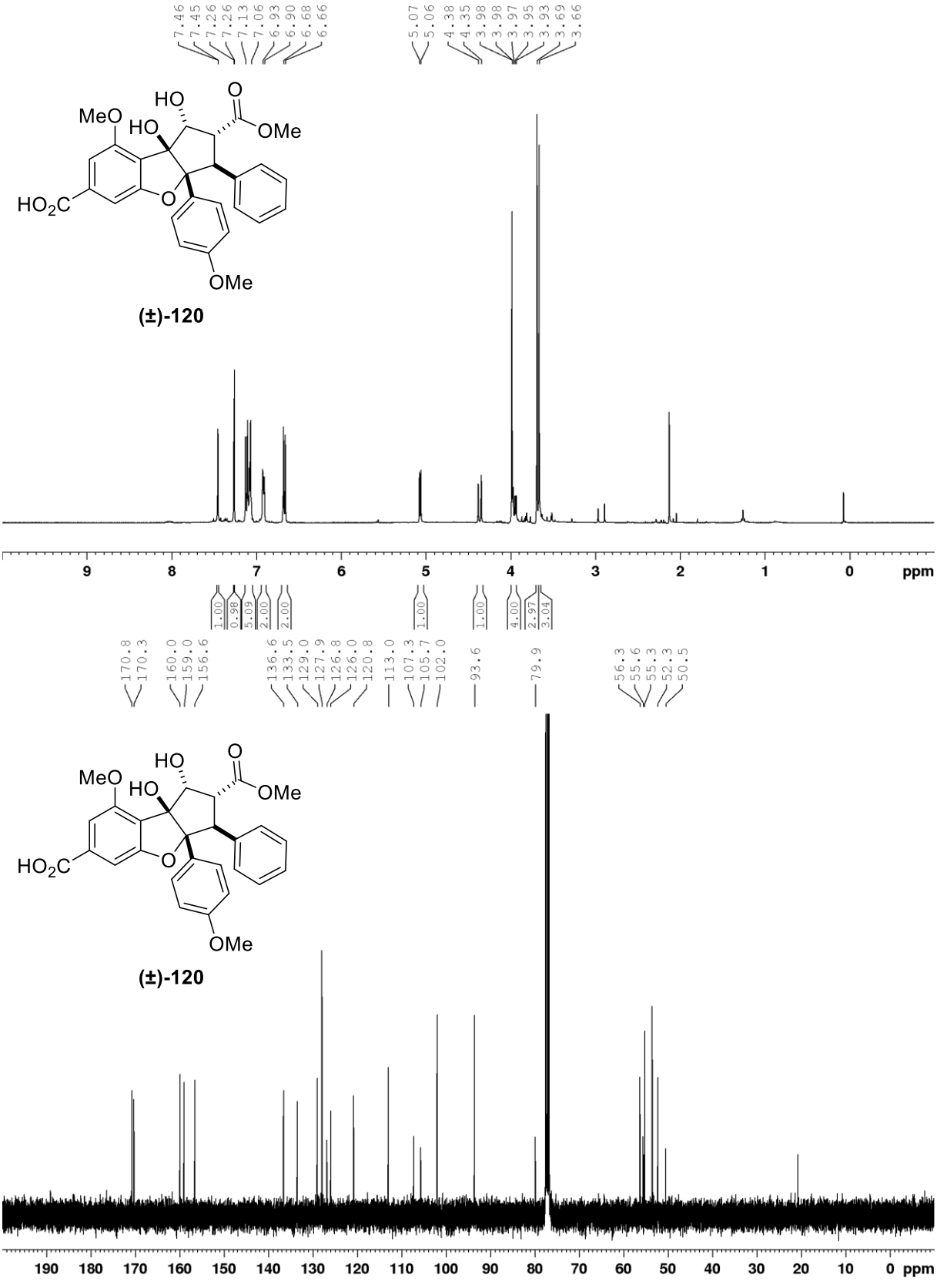
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-6-(((trifluoromethyl)sulfonyl)oxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (±)-119)



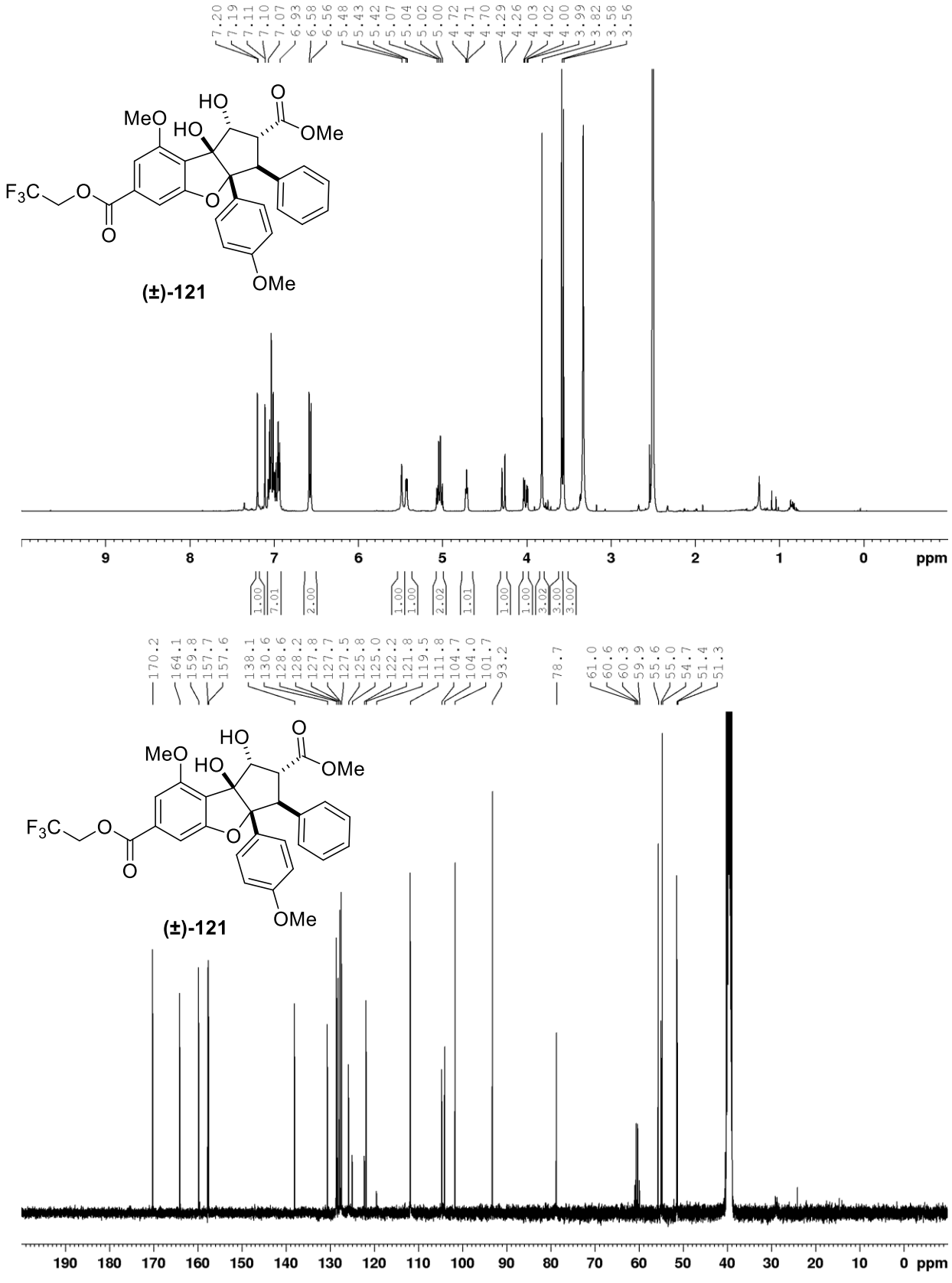
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-62)

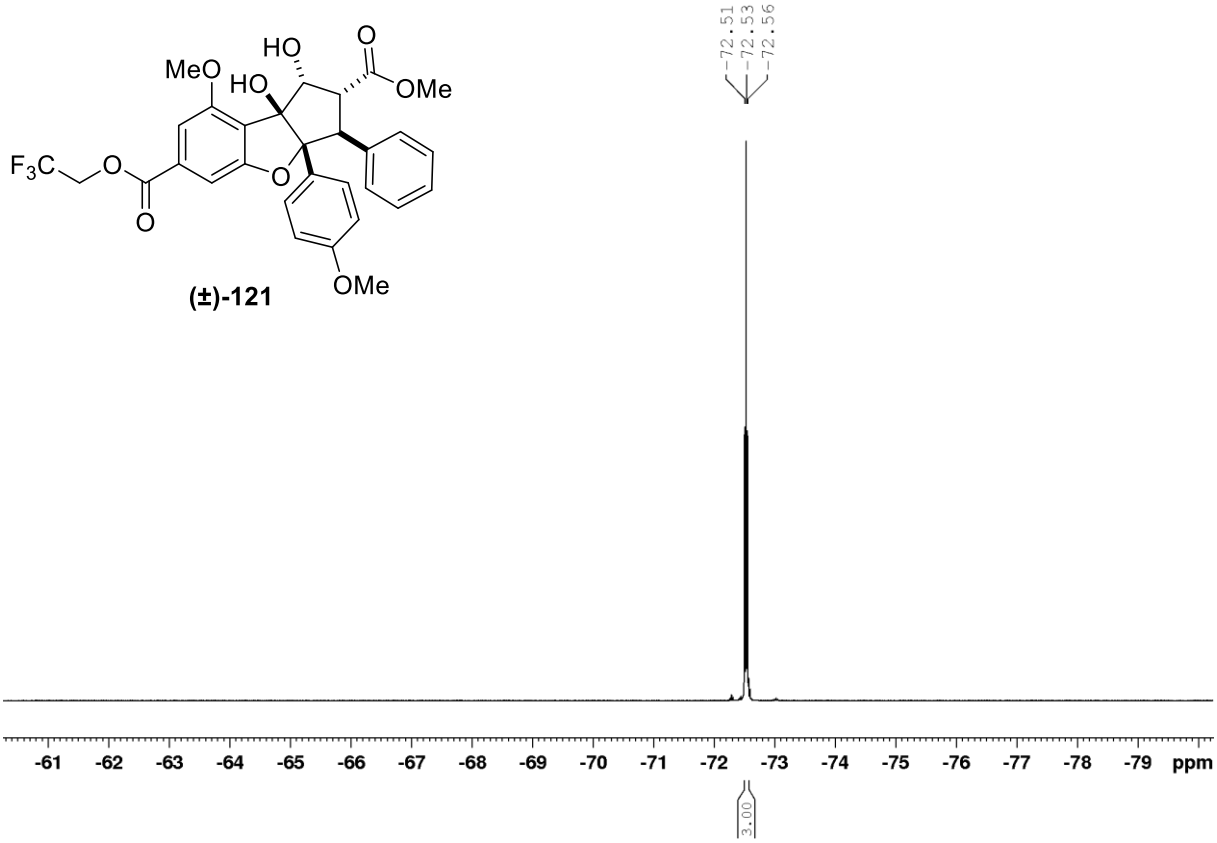


(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-2-(methoxycarbonyl)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-6-carboxylic acid ((±)-120)

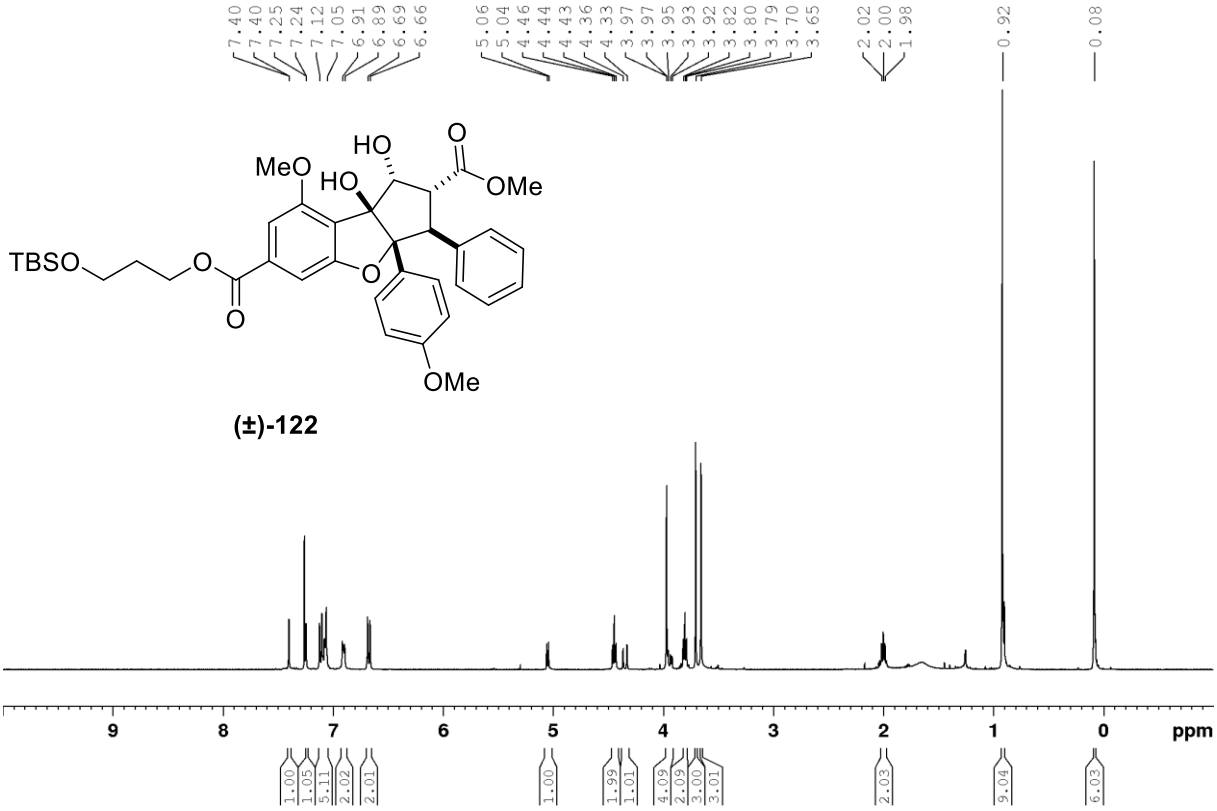


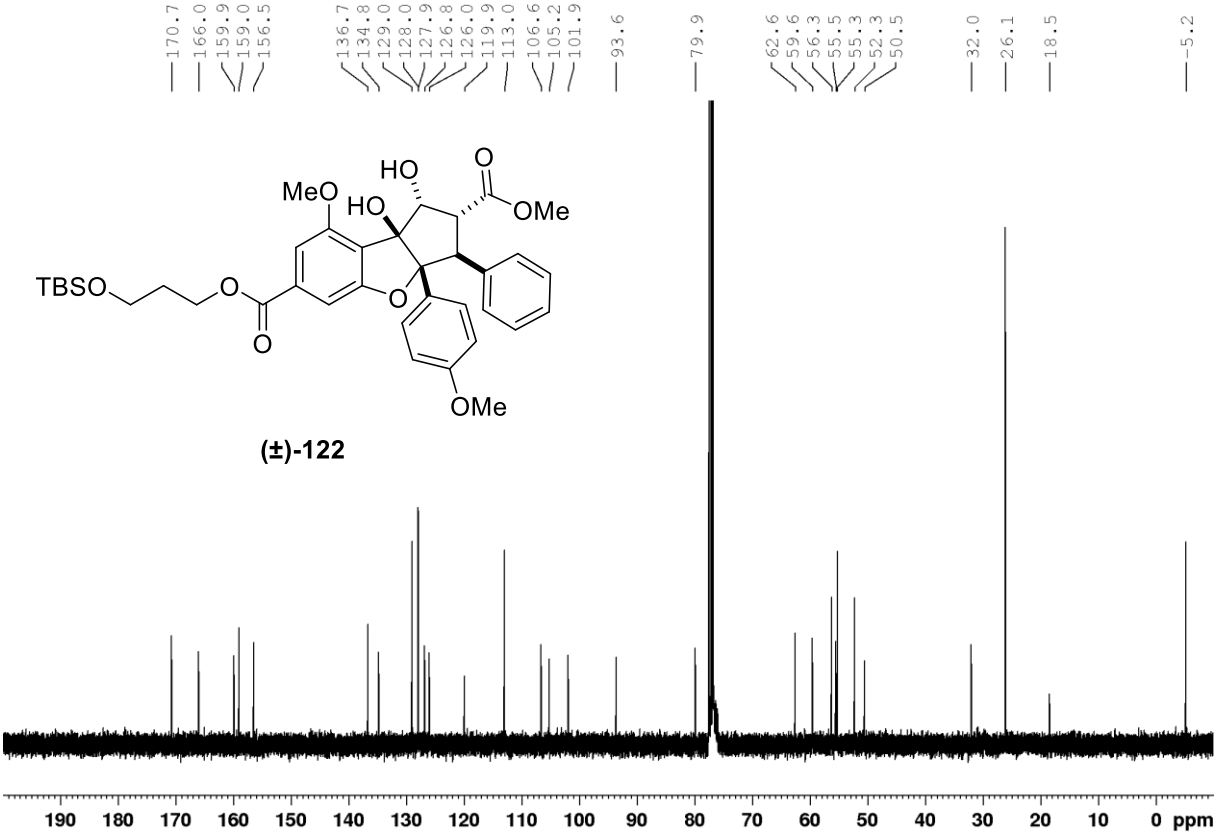
(±)-2-Methyl 6-(2,2,2-trifluoroethyl) (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-121)





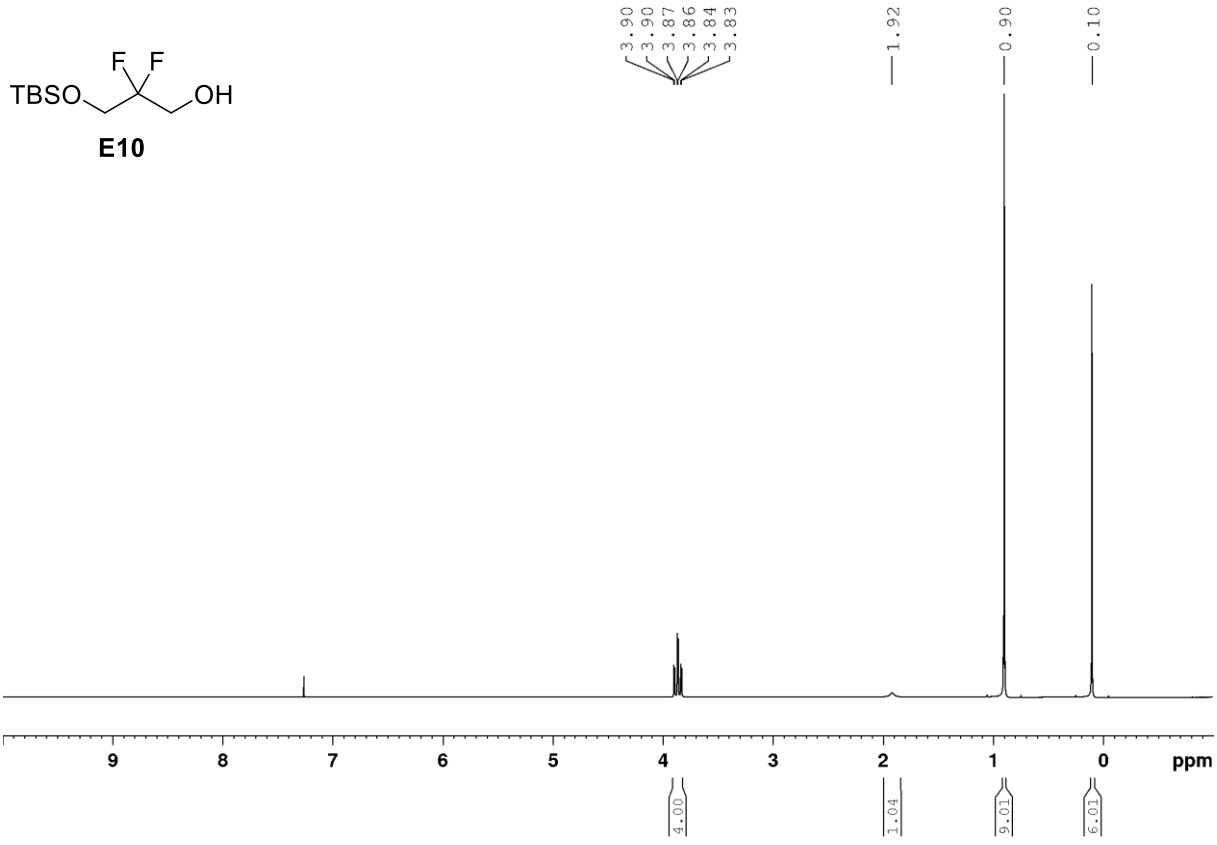
(±)-6-(4-((*tert*-Butyldimethylsilyl)oxy)butyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-122)



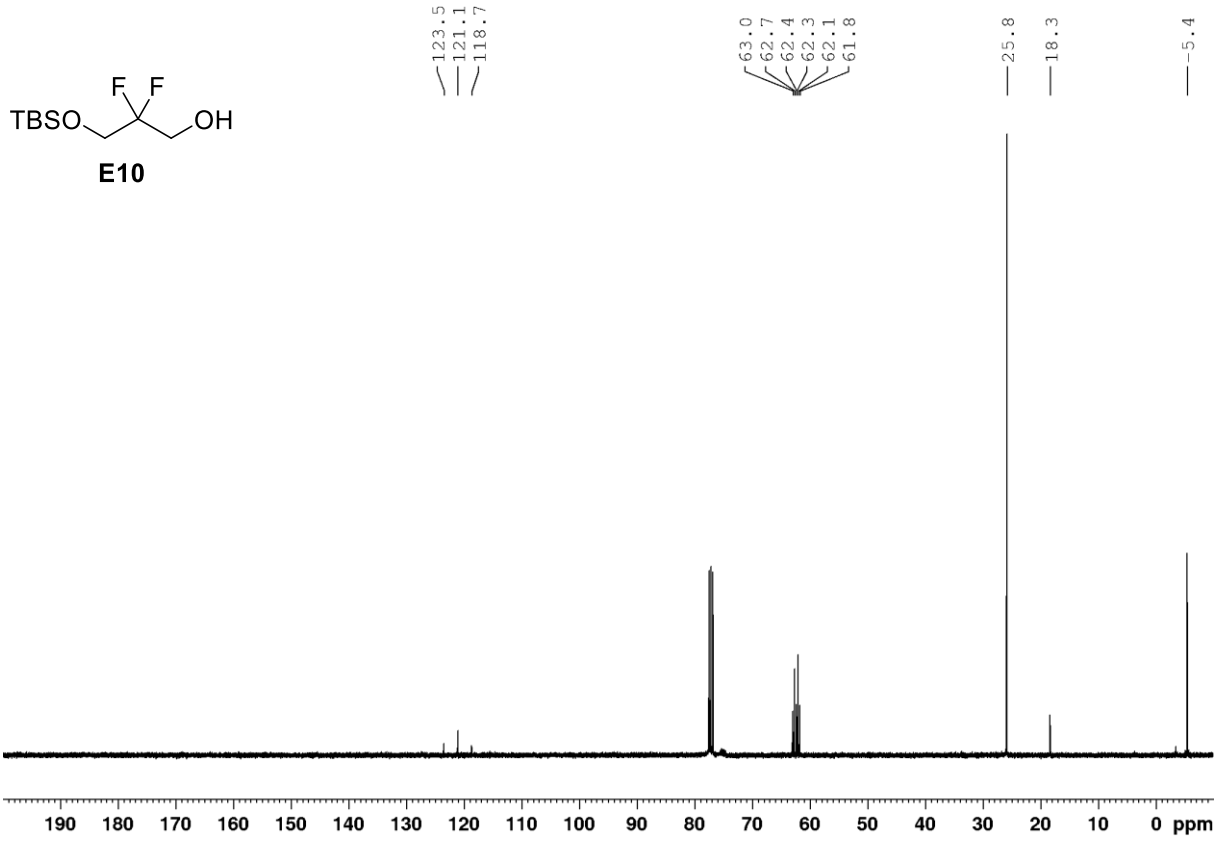


(±)-122

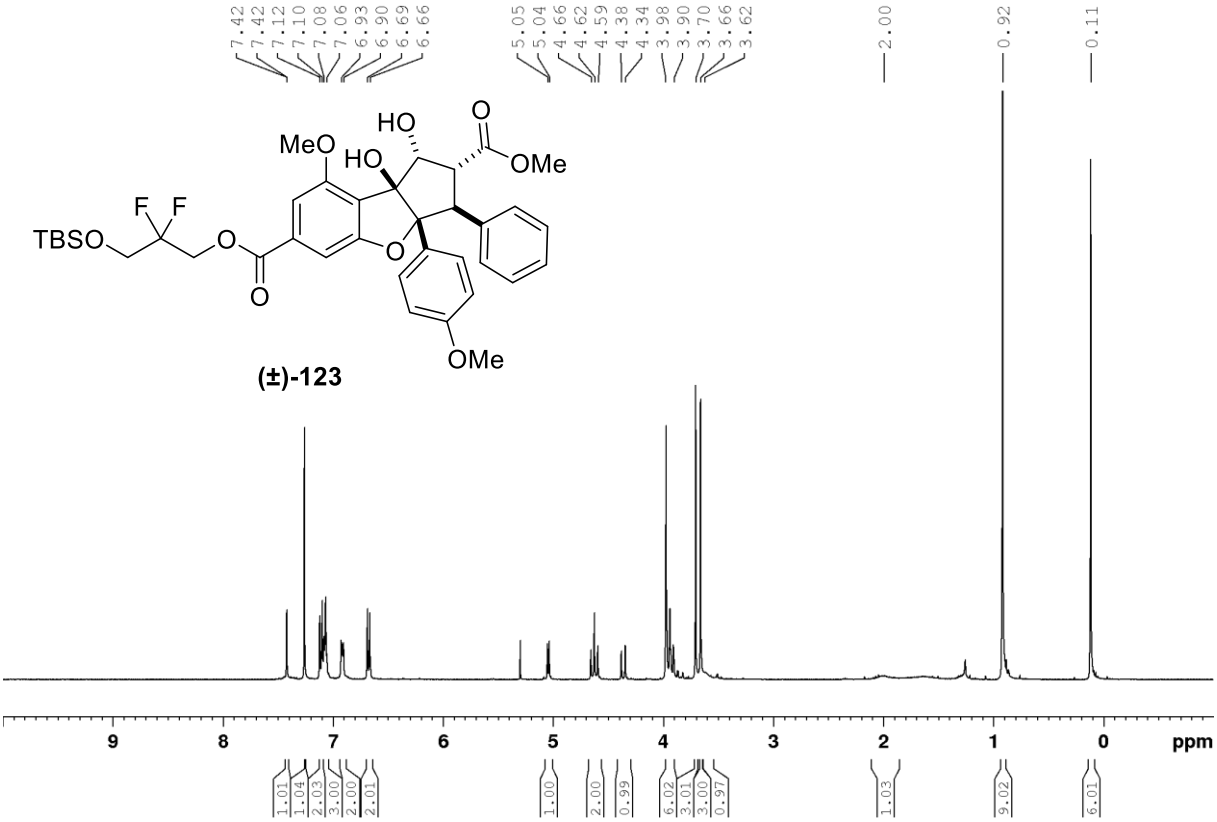
3-((*tert*-Butyldimethylsilyl)oxy)-2,2-difluoropropan-1-ol (E10)

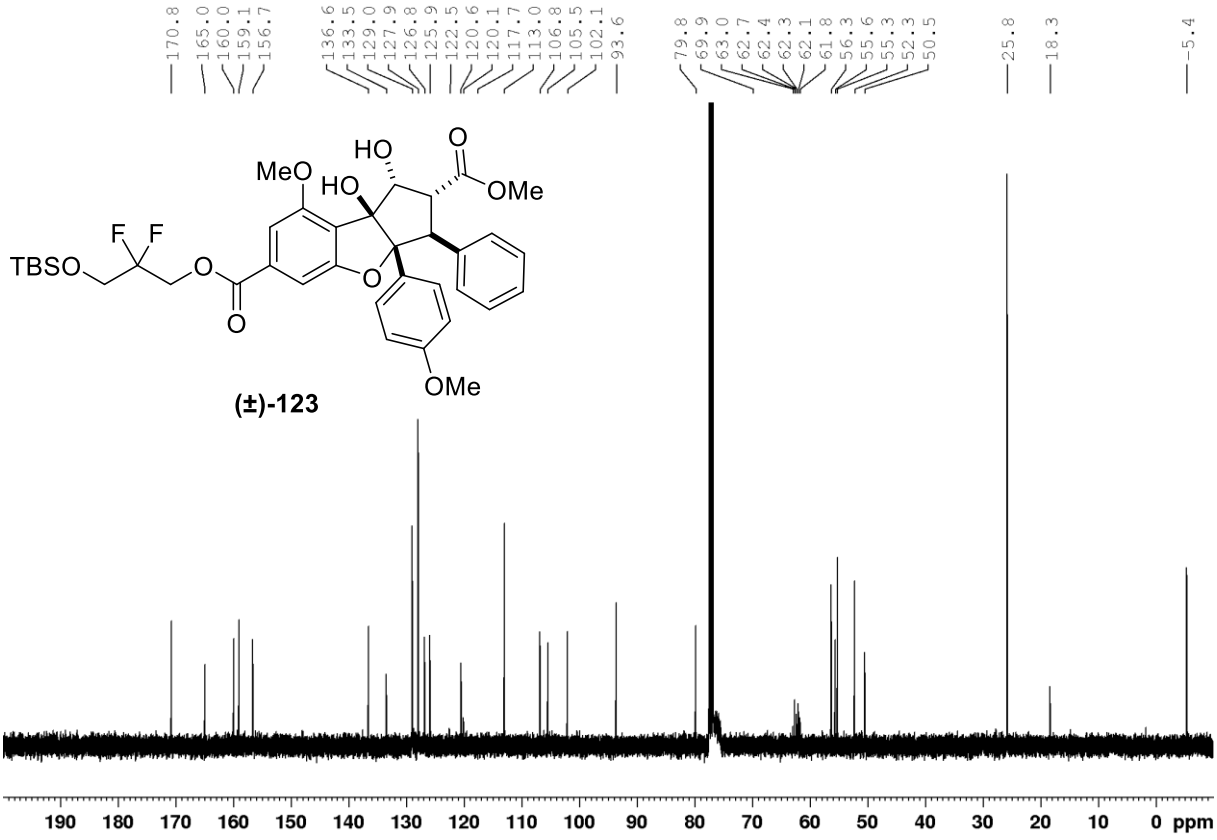


E10

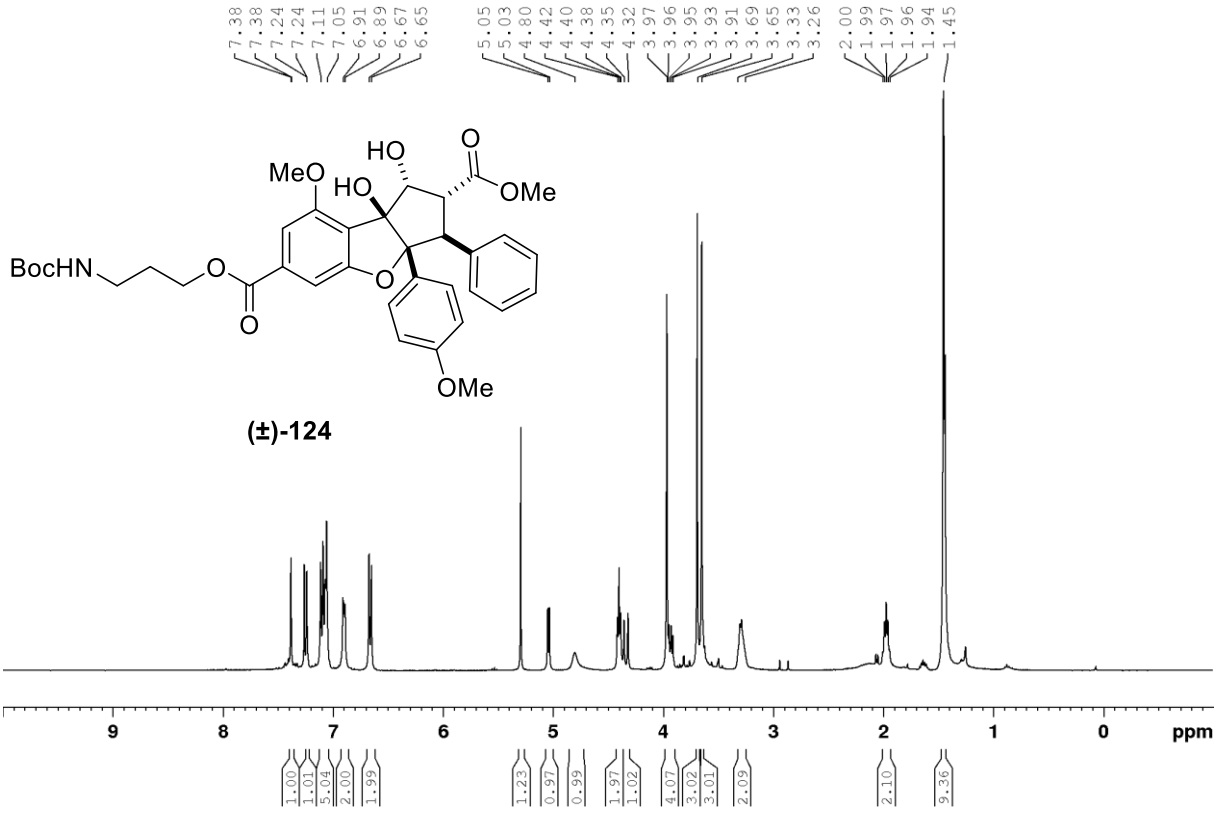


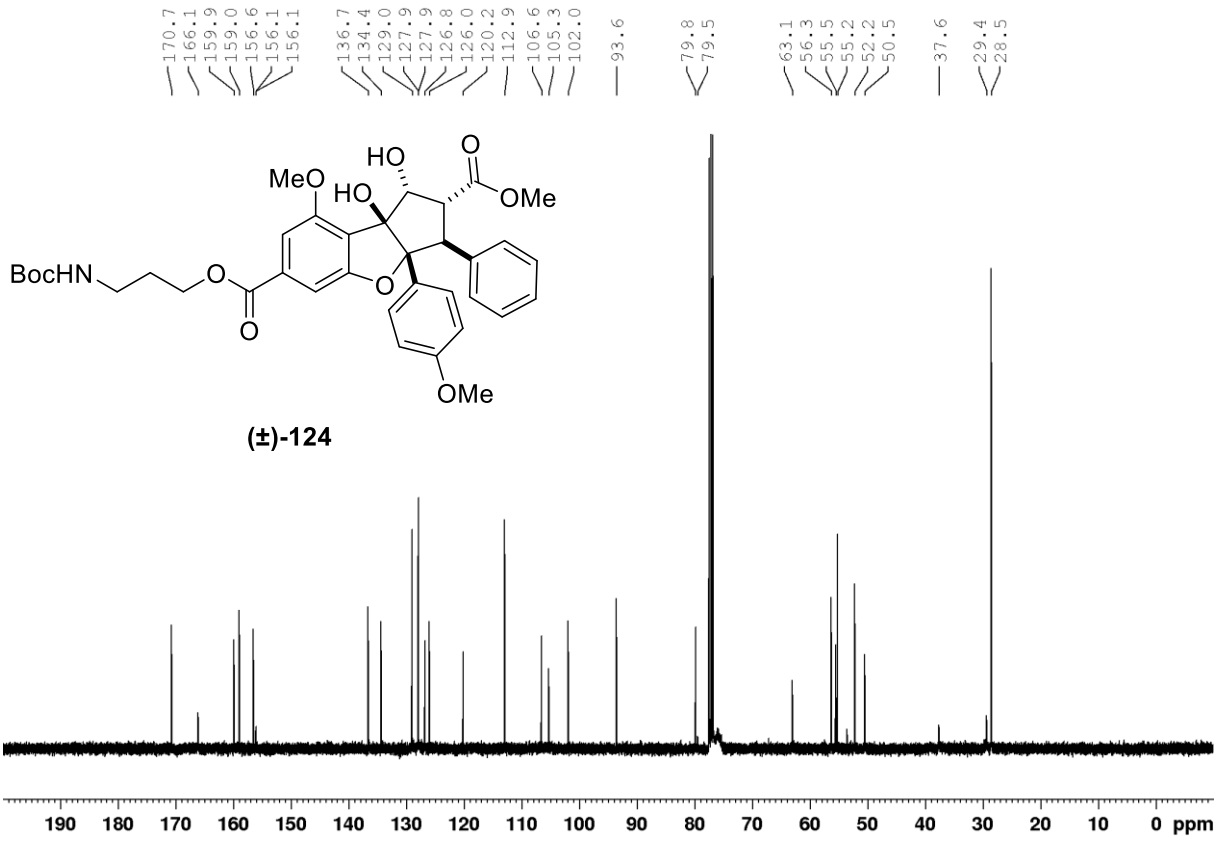
(±)-6-(3-((*tert*-Butyldimethylsilyl)oxy)-2,2-difluoropropyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-123)



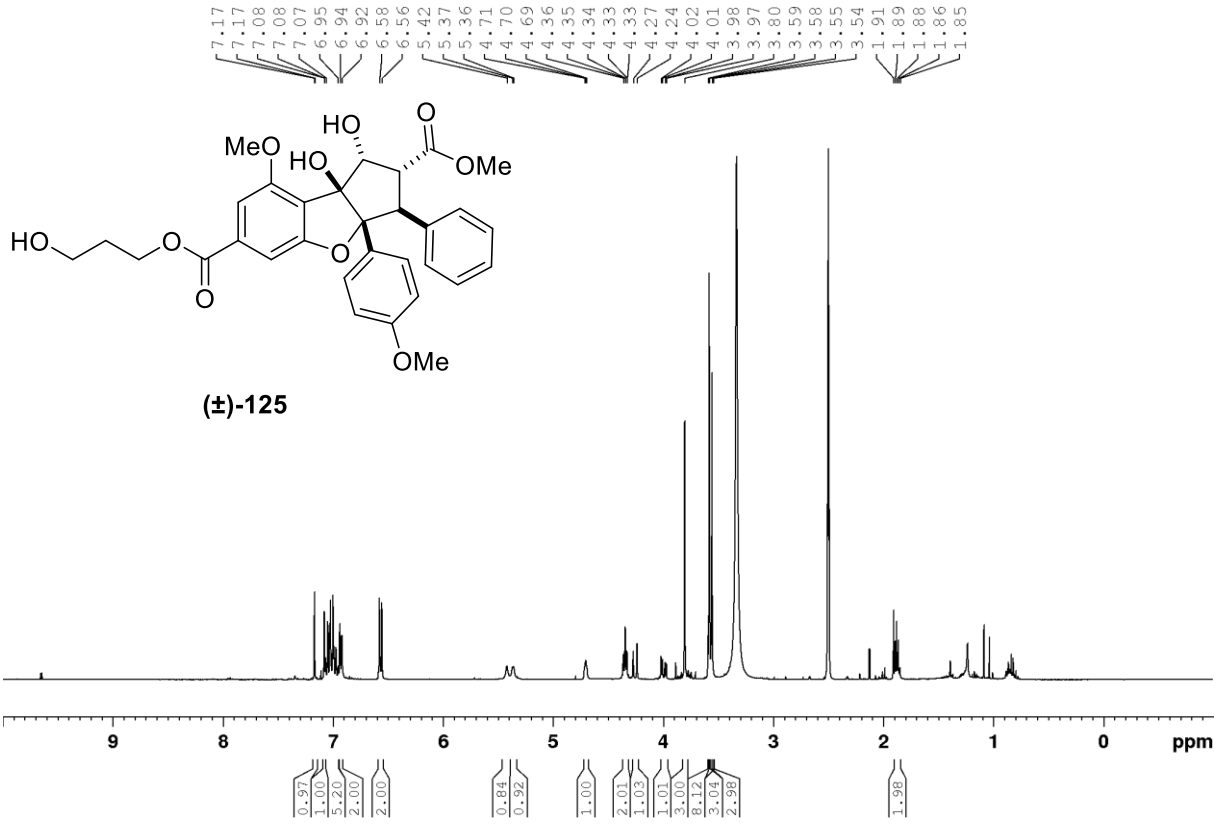


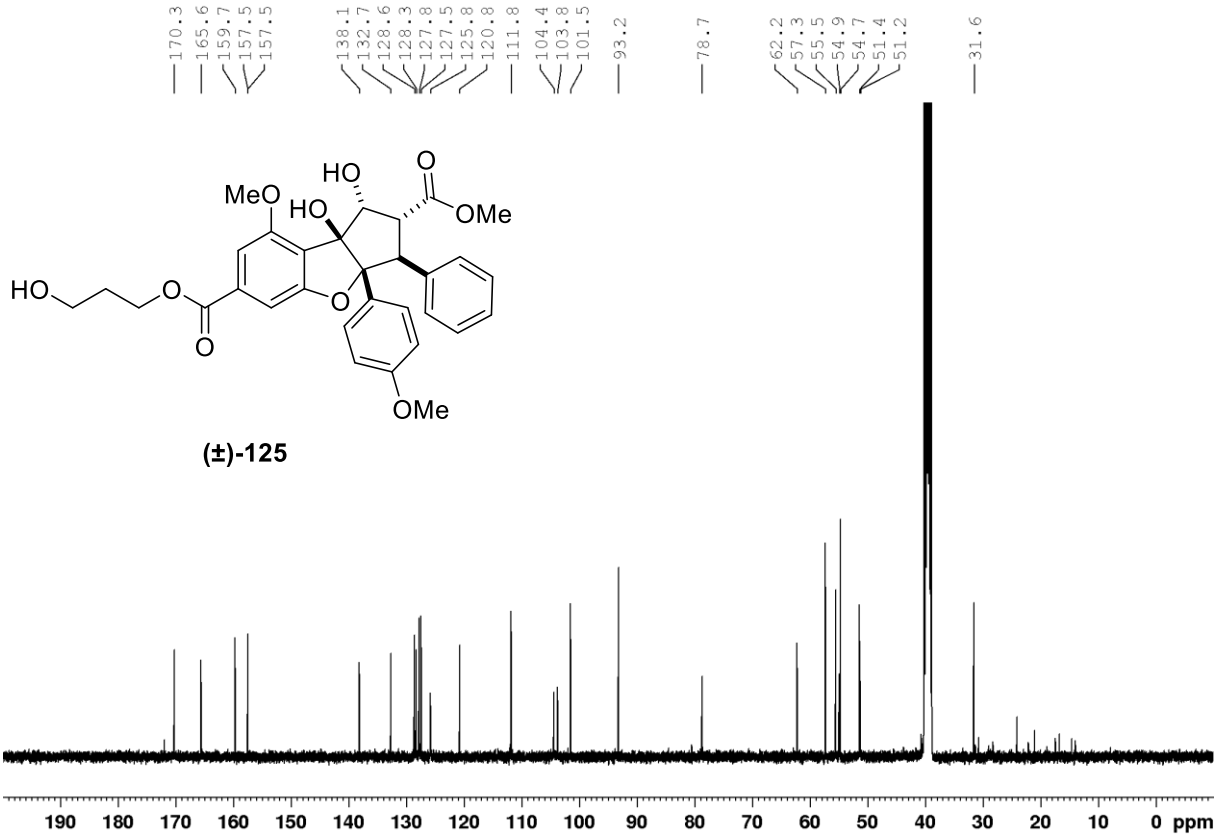
(±)-6-(3-((*tert*-Butoxycarbonyl)amino)propyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*] benzofuran-2,6-dicarboxylate ((±)-124)





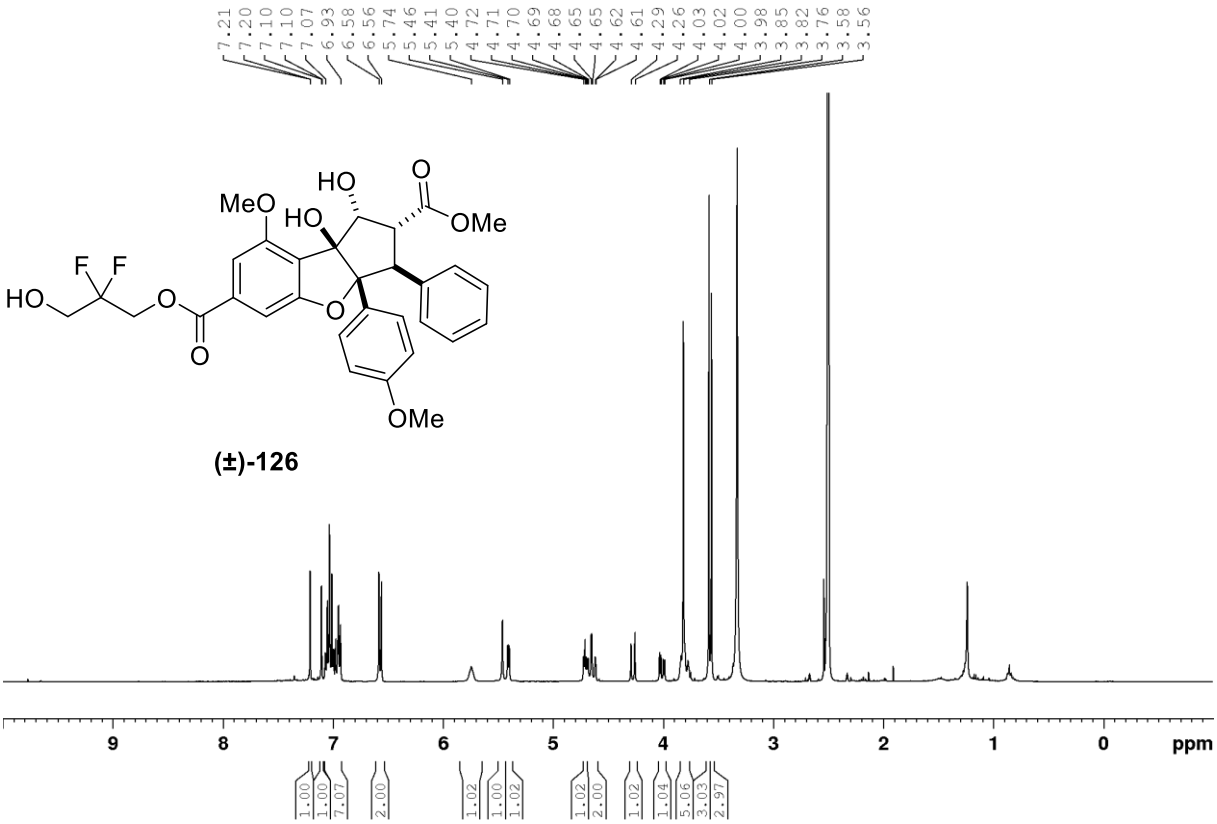
(±)-6-(3-Hydroxypropyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2,6-dicarboxylate ((±)-125)



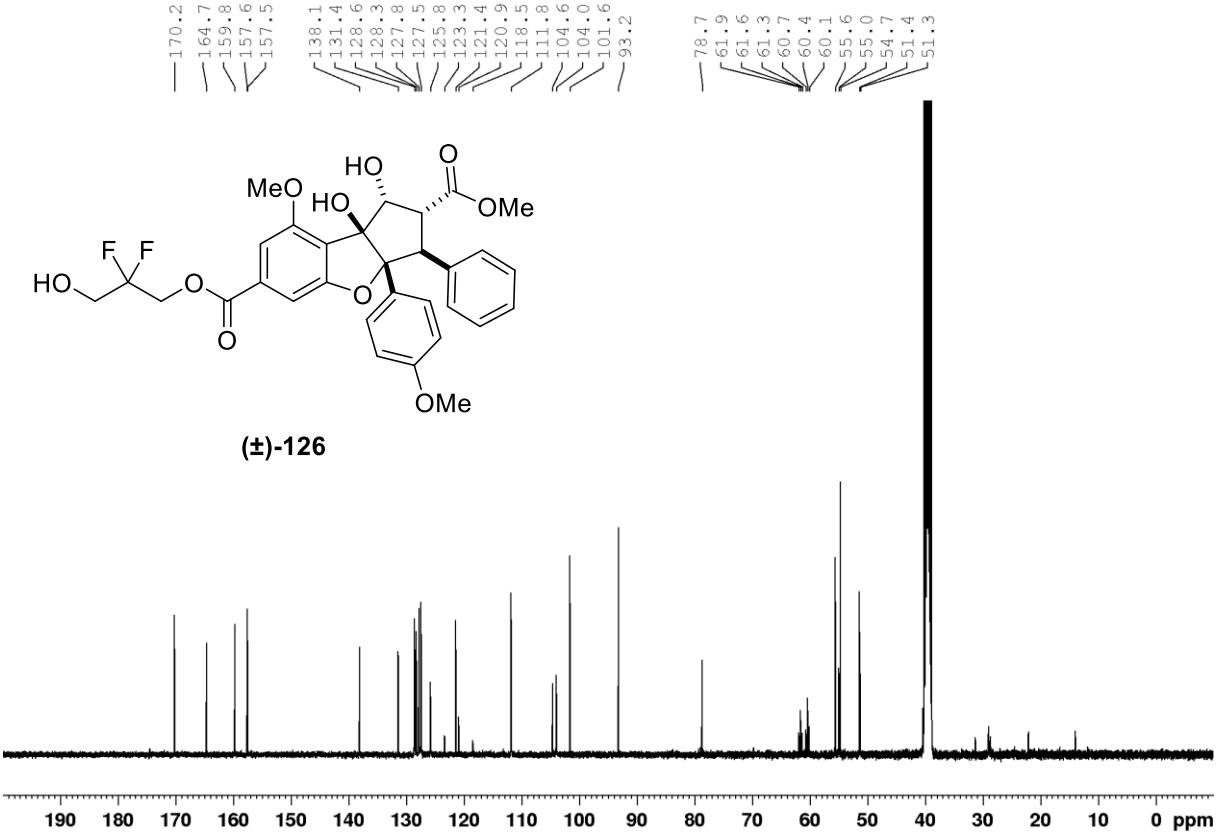


(±)-125

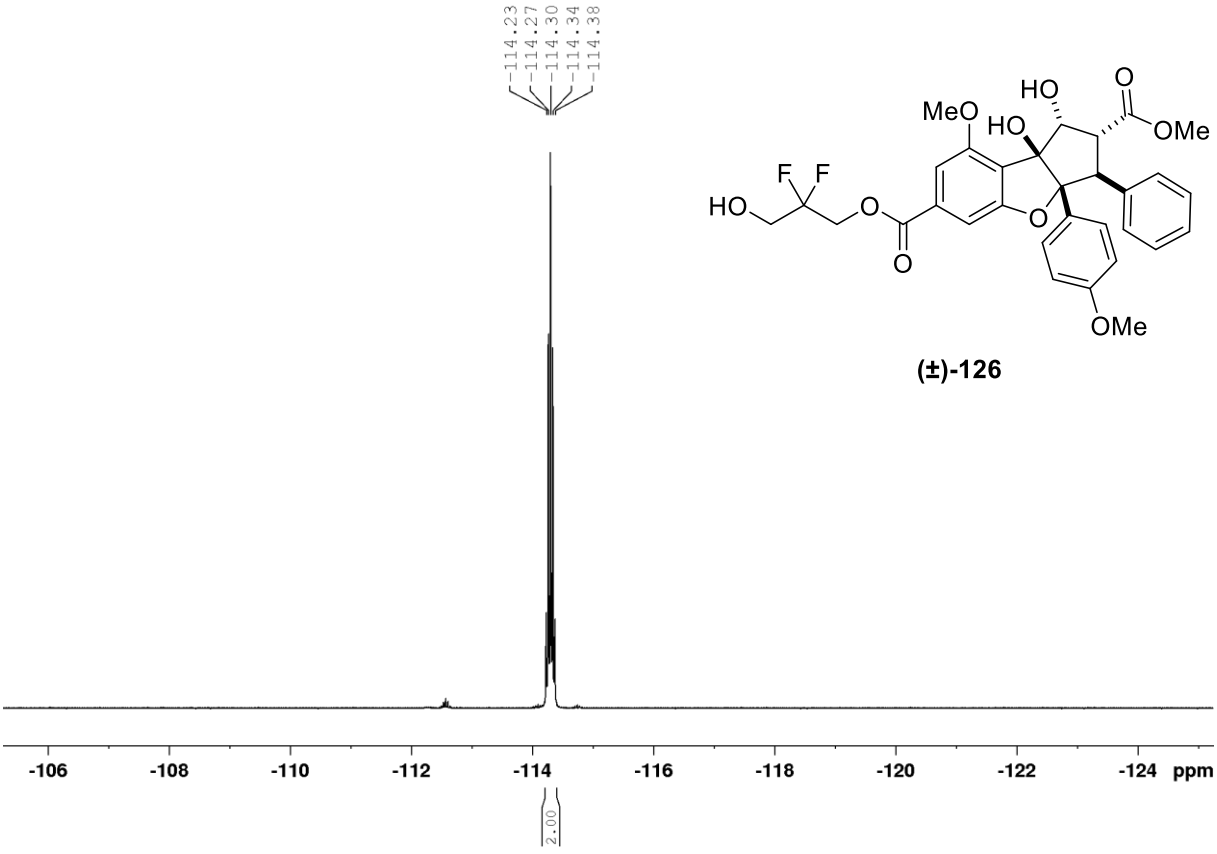
(±)-6-(2,2-Difluoro-3-hydroxypropyl) 2-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzo-furan-2,6-dicarboxylate ((±)-126)



(±)-126

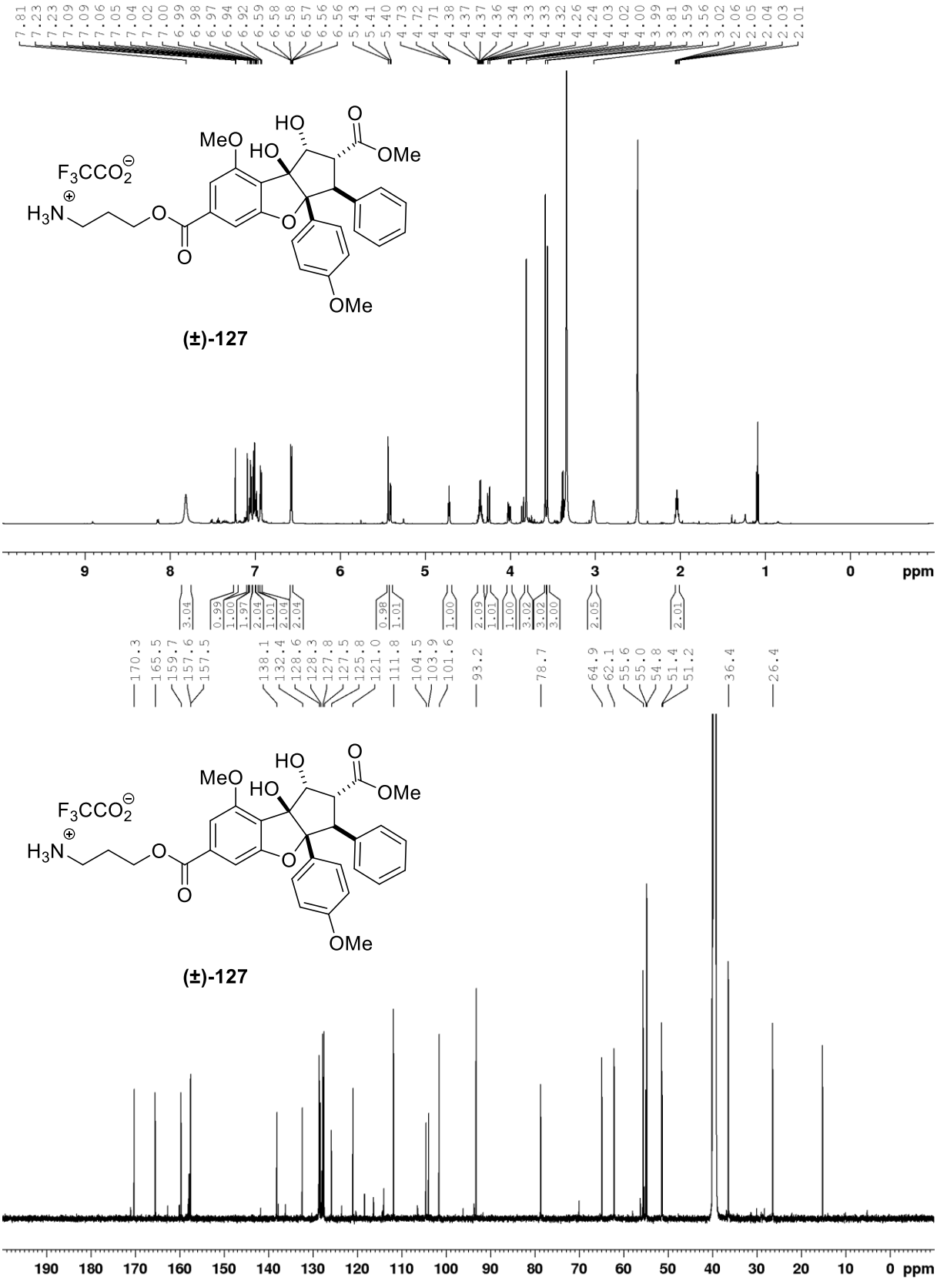

170.2
164.7
159.8
157.6
157.5
138.1
131.4
128.6
128.3
127.8
127.5
125.8
123.3
121.4
120.9
118.5
111.8
104.6
104.0
101.6
93.2
78.7
61.9
61.6
61.3
60.7
60.4
60.1
55.6
55.0
54.7
51.4
51.3
HO
O
MeO
HO
OMe
F F
HO
O
O
O
OMe
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

(±)-126

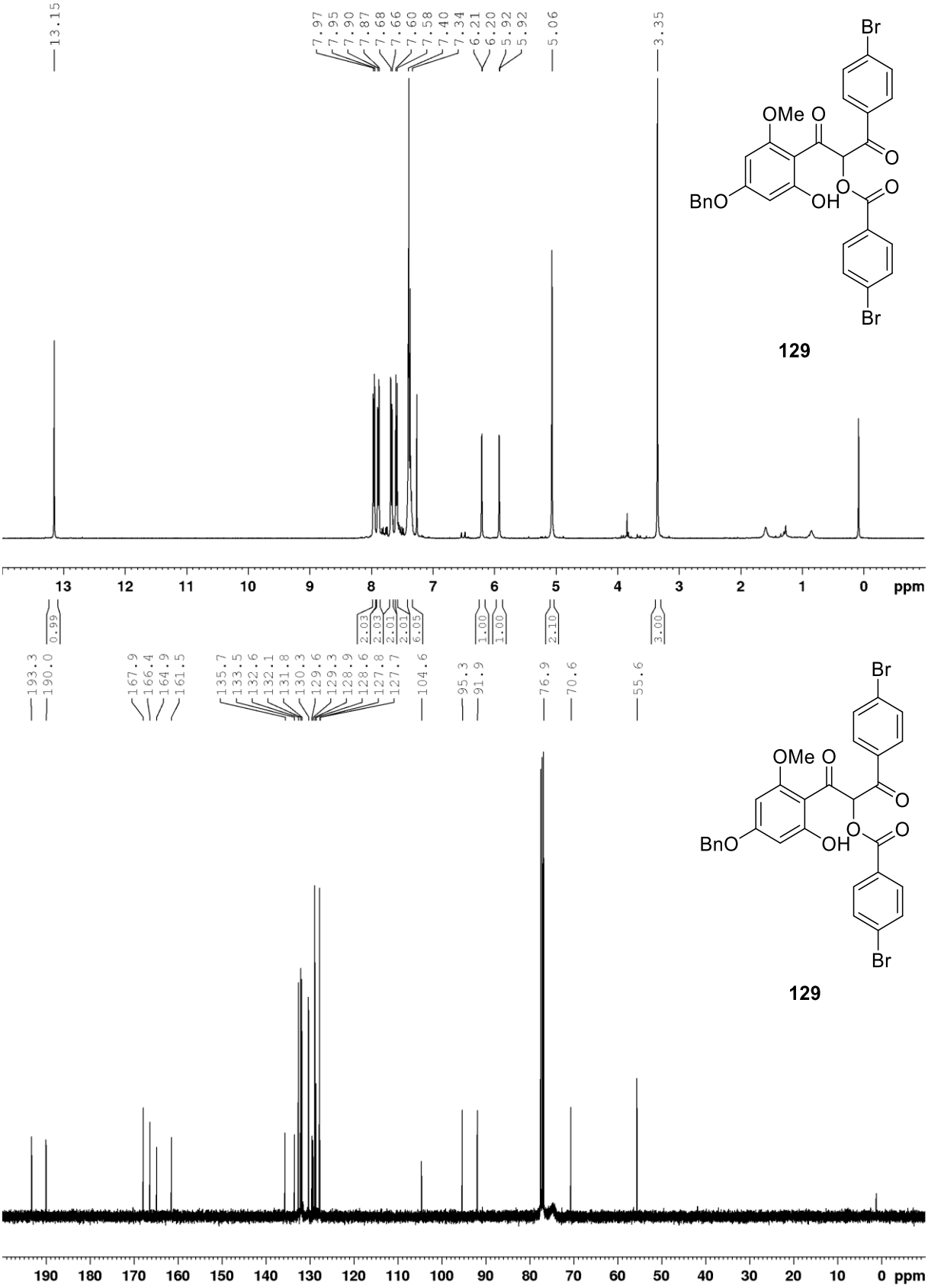

114.23
114.27
114.30
114.34
114.38
HO
O
MeO
HO
OMe
F F
HO
O
O
O
OMe
-106 -108 -110 -112 -114 -116 -118 -120 -122 -124 ppm
2.00

(±)-126

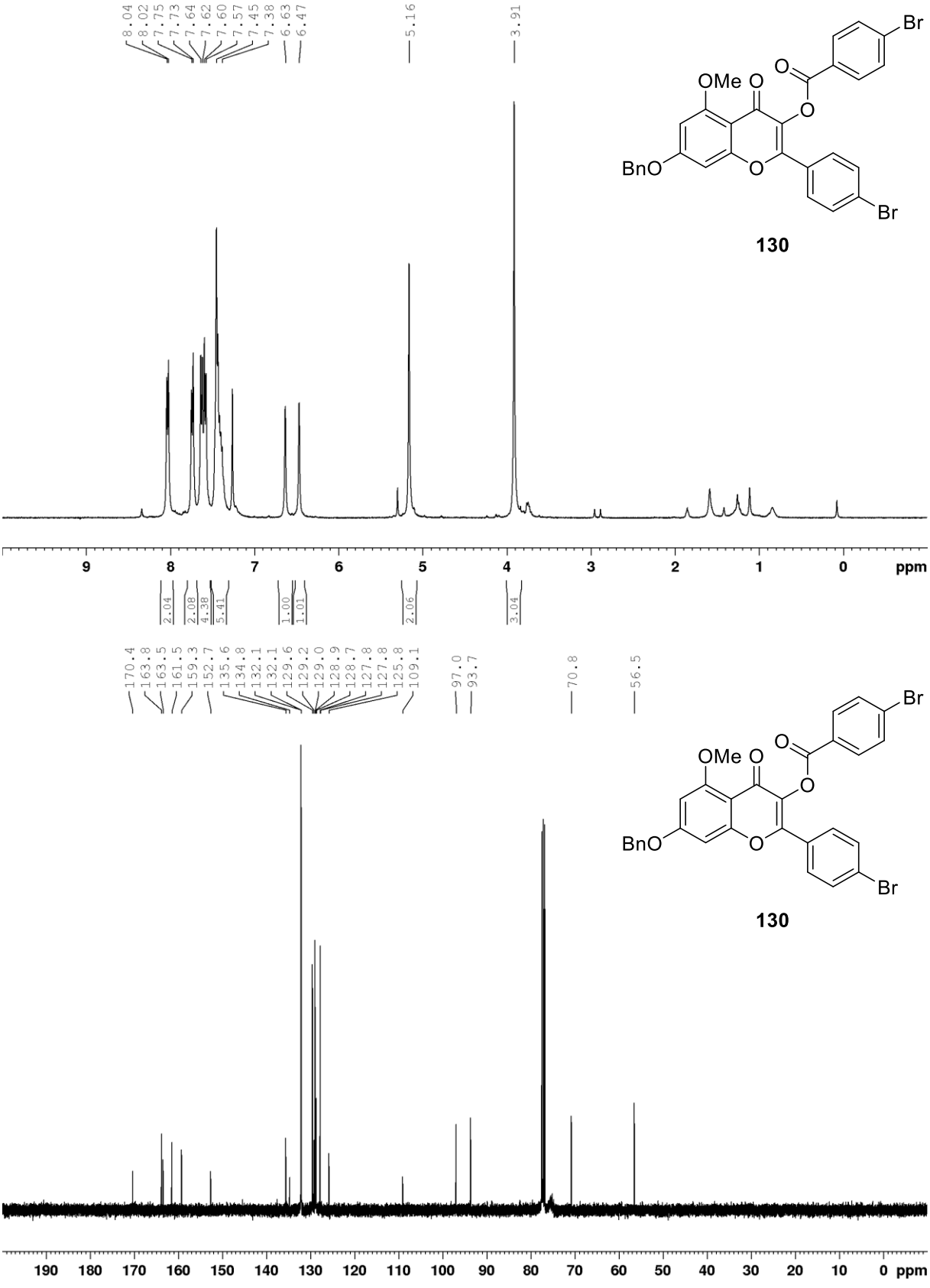
(±)-3-(((1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-8-methoxy-2-(methoxycarbonyl)-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-6-carbonyl)oxy)propan-1-aminium 2,2,2-trifluoroacetate ((±)-127)



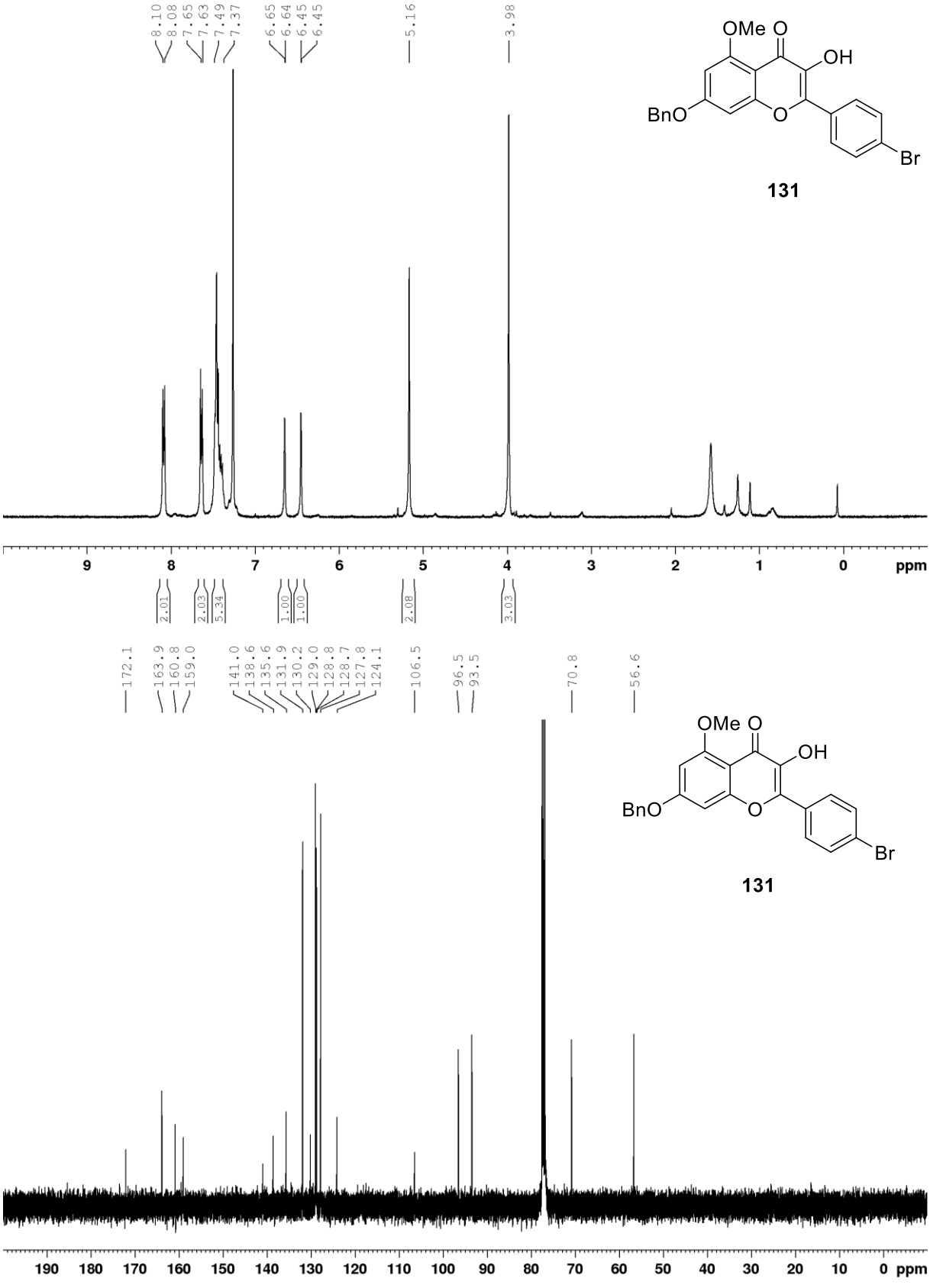
1-(4-(Benzyloxy)-2-hydroxy-6-methoxyphenyl)-3-(4-bromophenyl)-1,3-dioxopropan-2-yl 4-bromobenzoate (129)



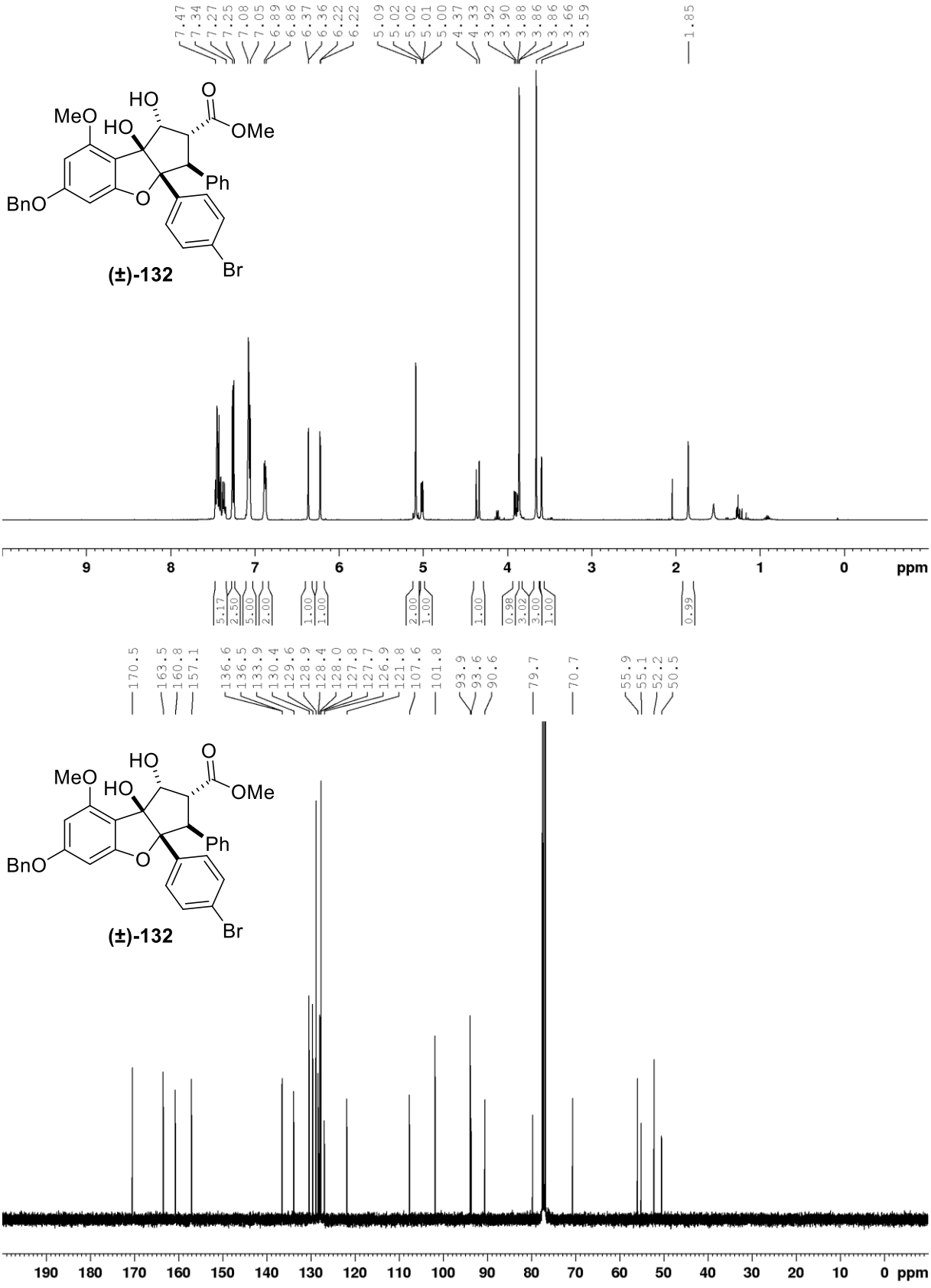
7-(Benzyloxy)-2-(4-bromophenyl)-5-methoxy-4-oxo-4*H*-chromen-3-yl 4-bromobenzoate (130)



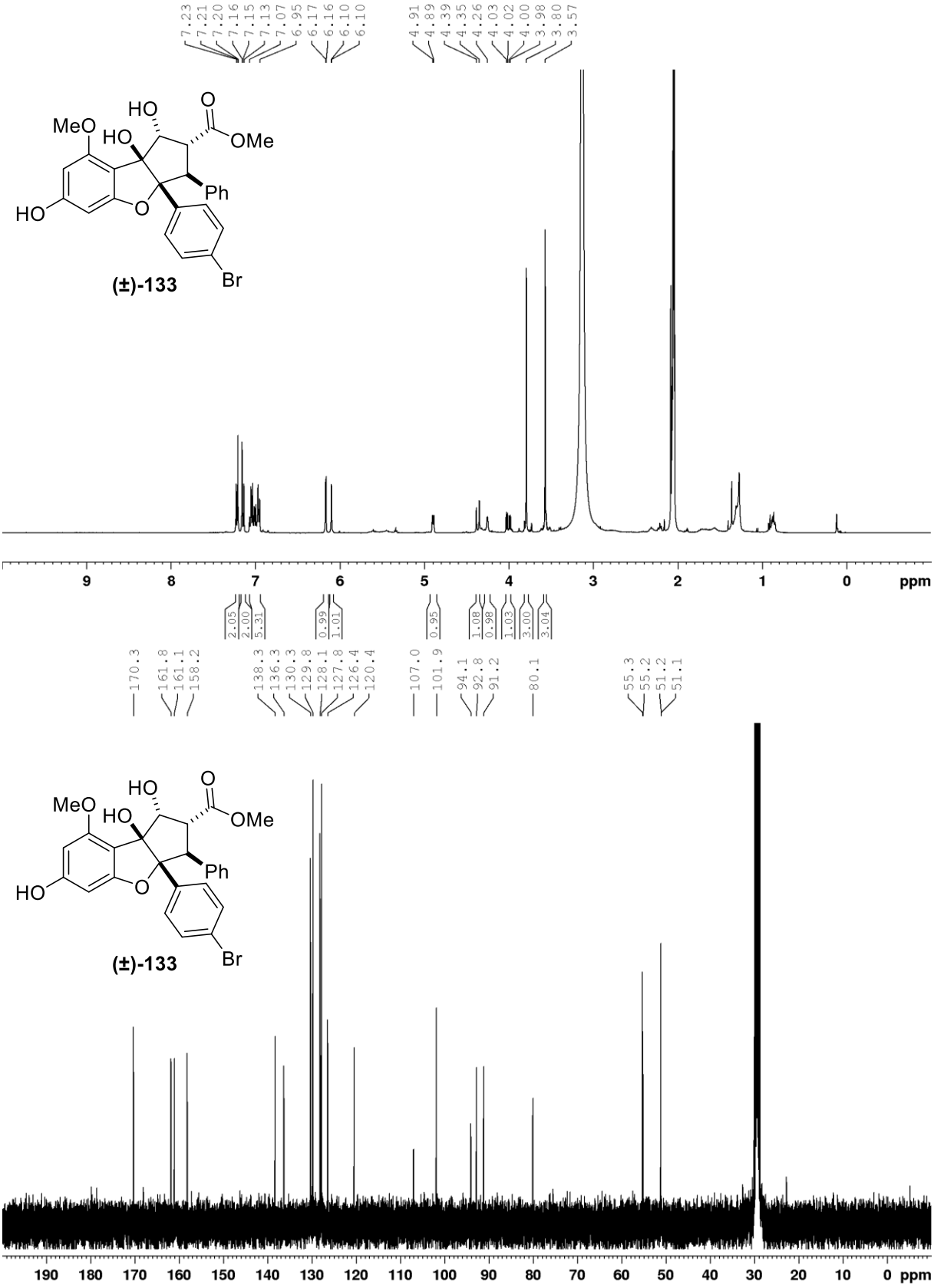
7-(Benzyloxy)-2-(4-bromophenyl)-3-hydroxy-5-methoxy-4*H*-chromen-4-one (131)



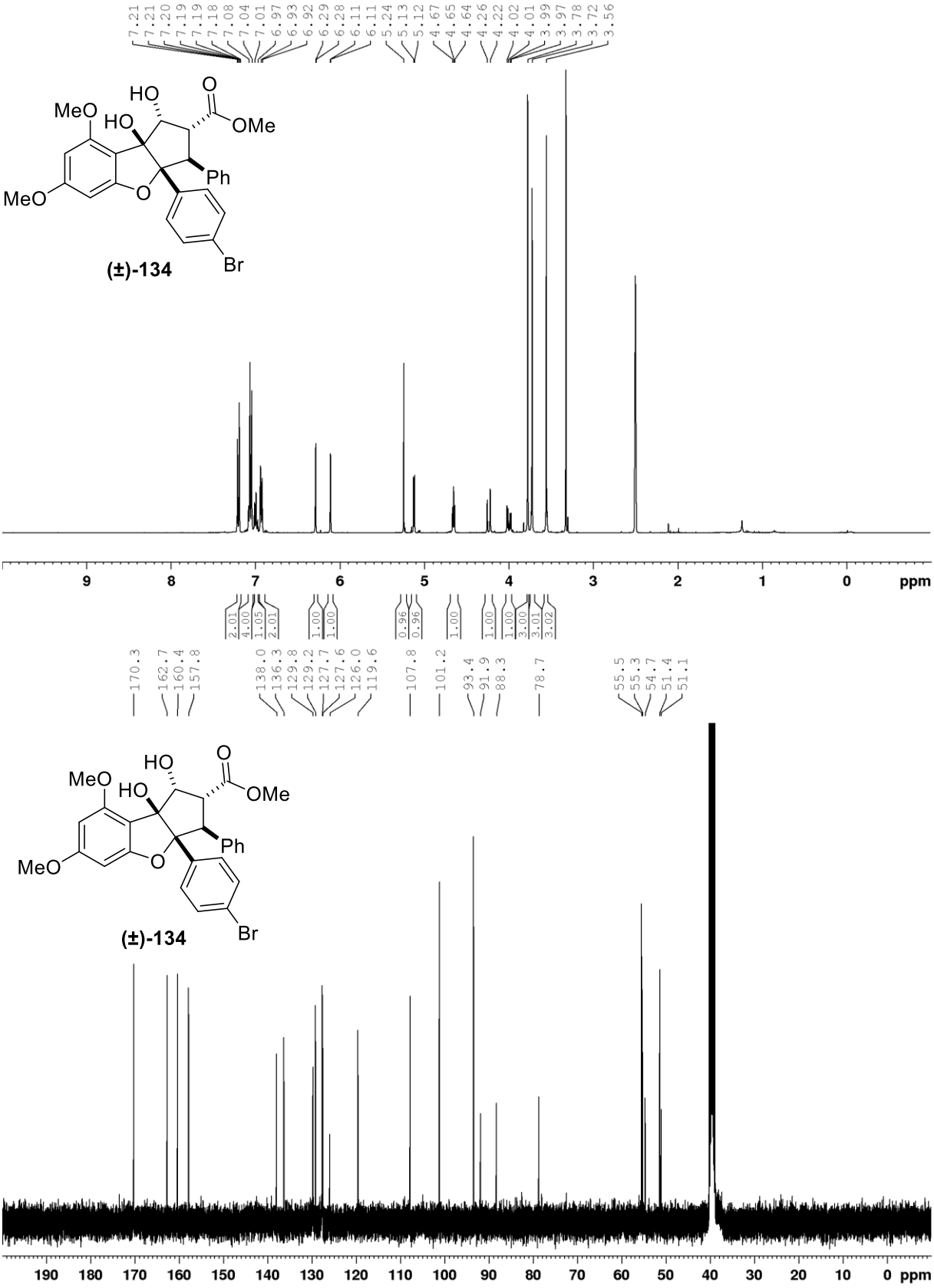
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(Benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-8-methoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-132)



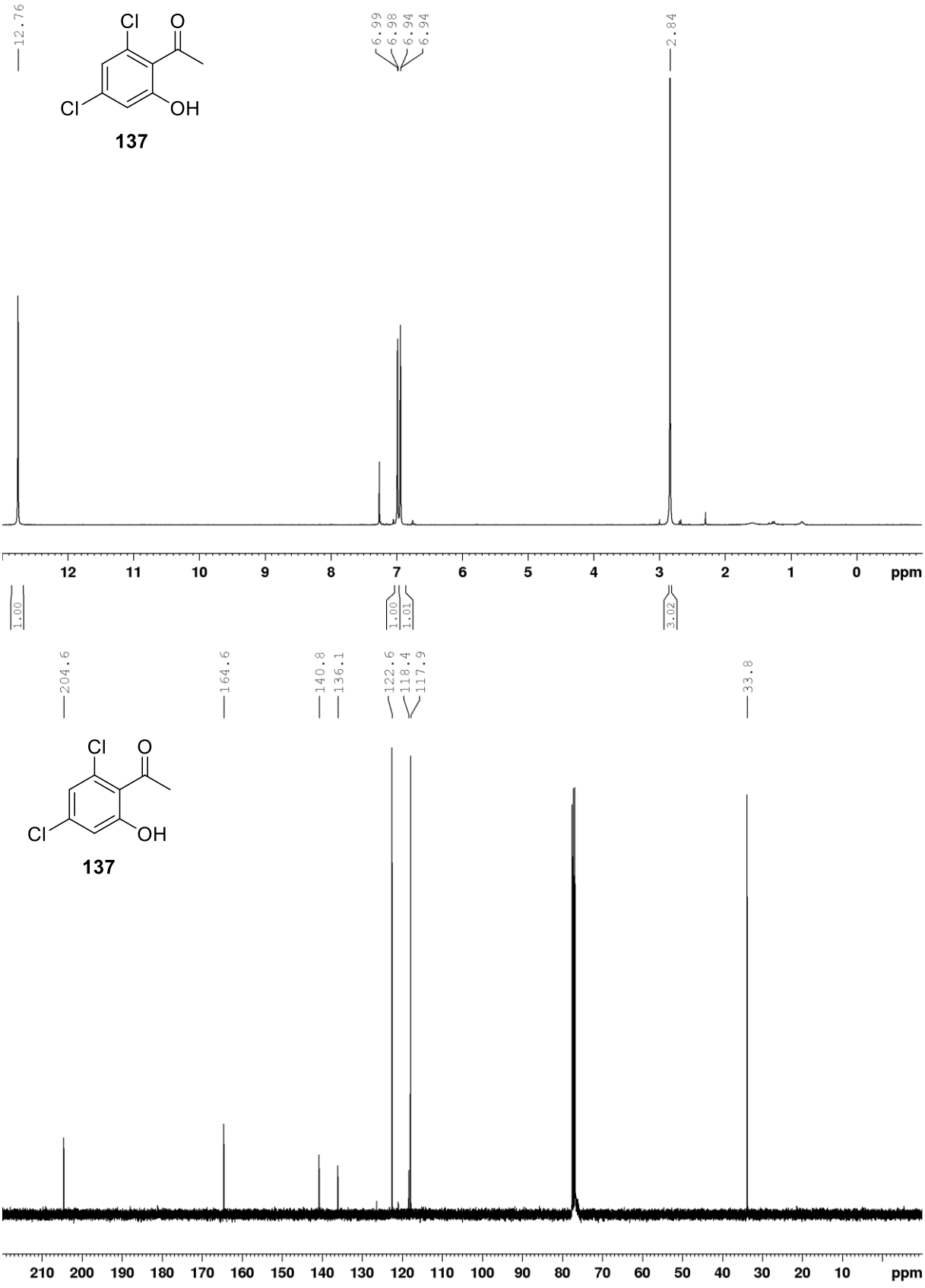
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,6,8b-trihydroxy-8-methoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-133)



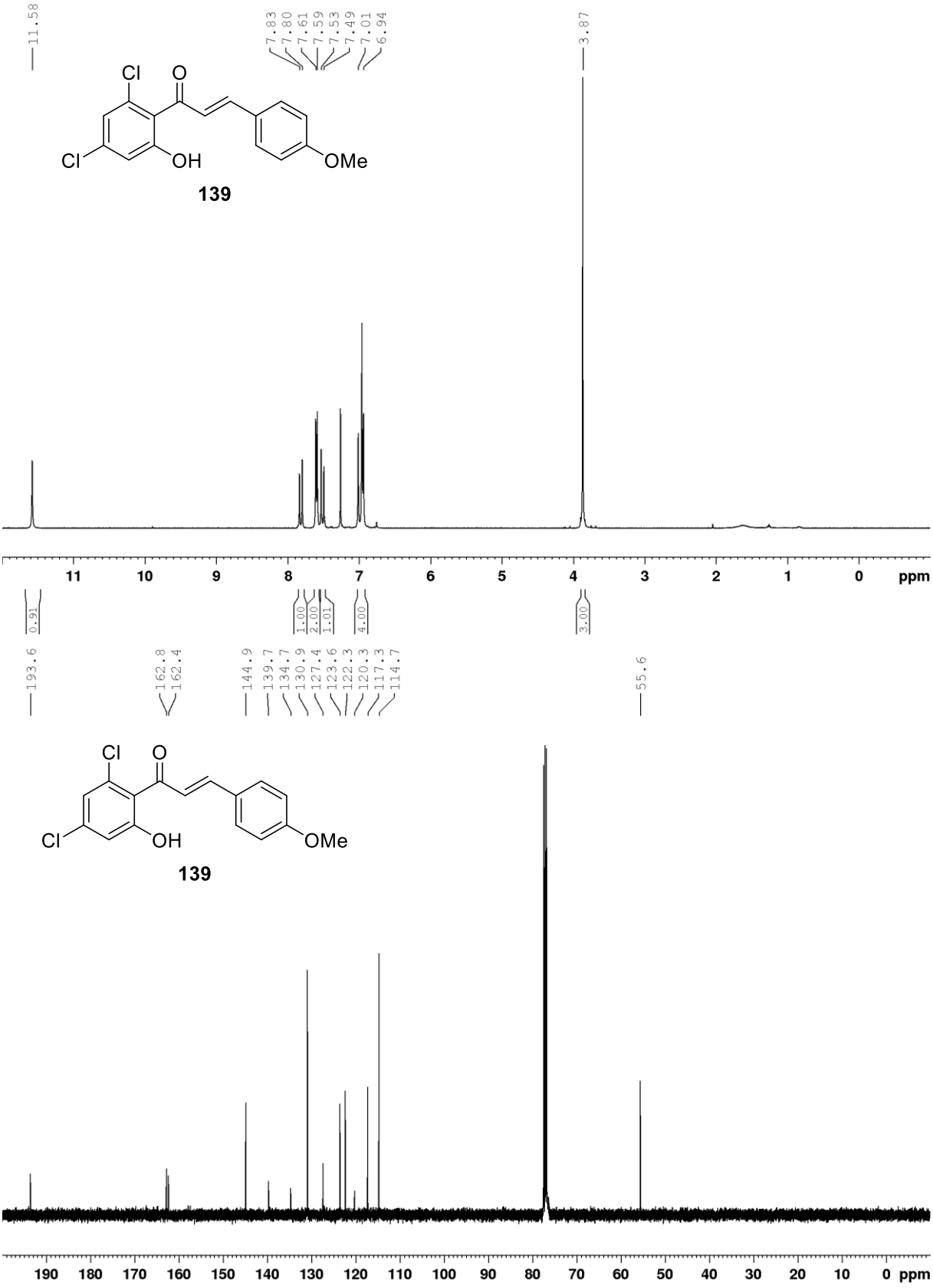
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-134)



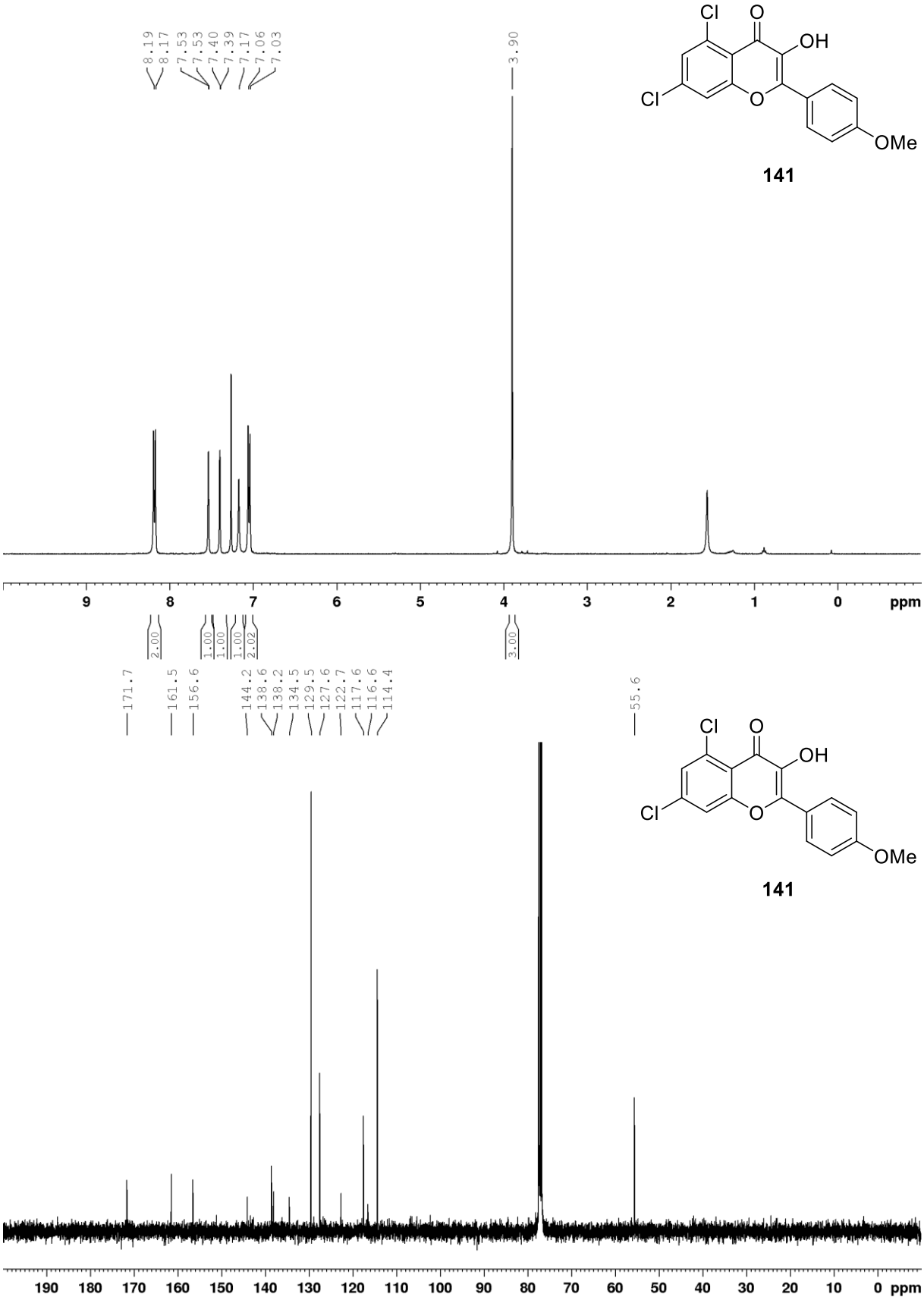
1-(2,4-Dichloro-6-hydroxyphenyl)ethan-1-one (137)



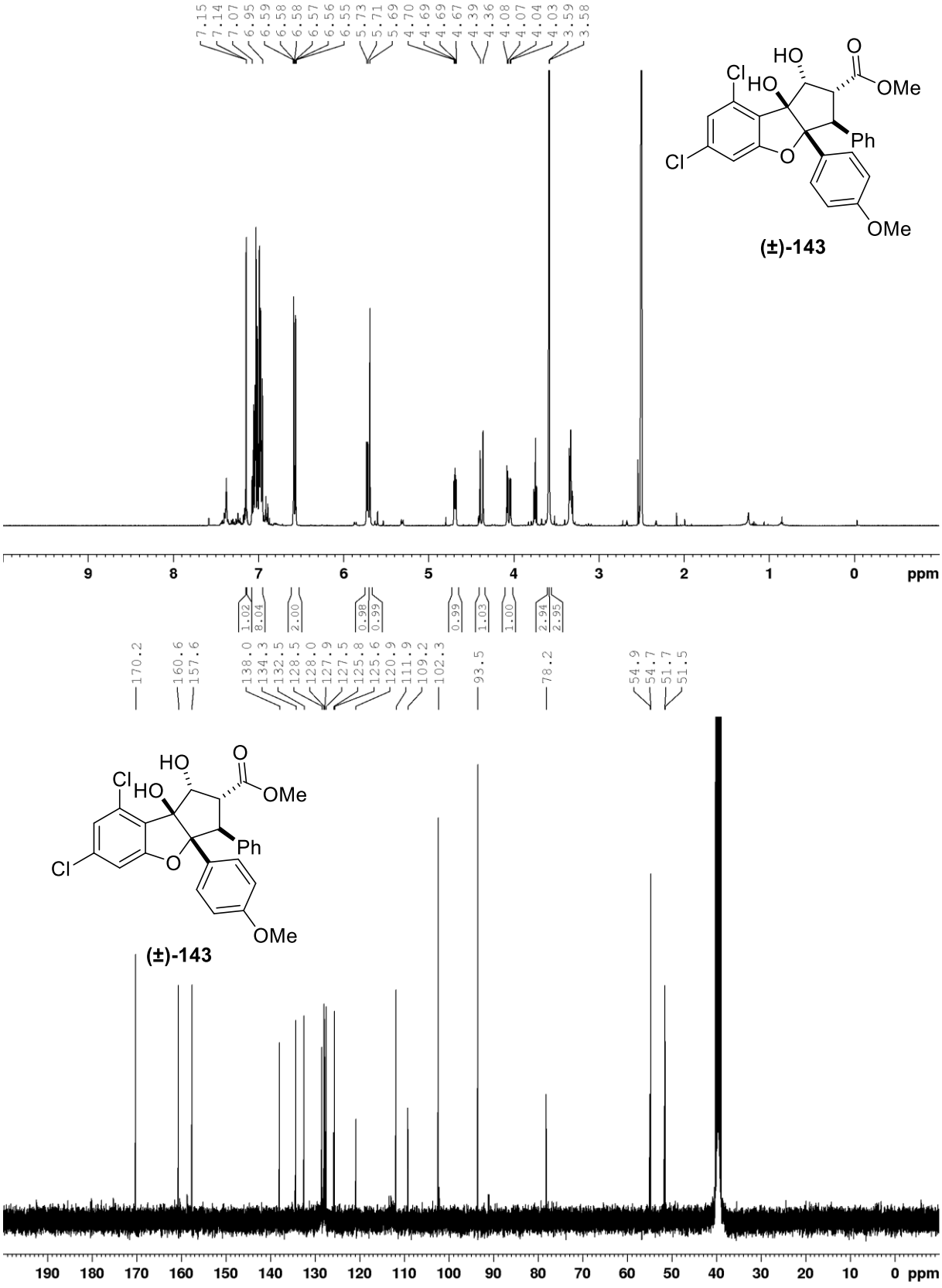
(*E*)-1-(2,4-Dichloro-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (139)



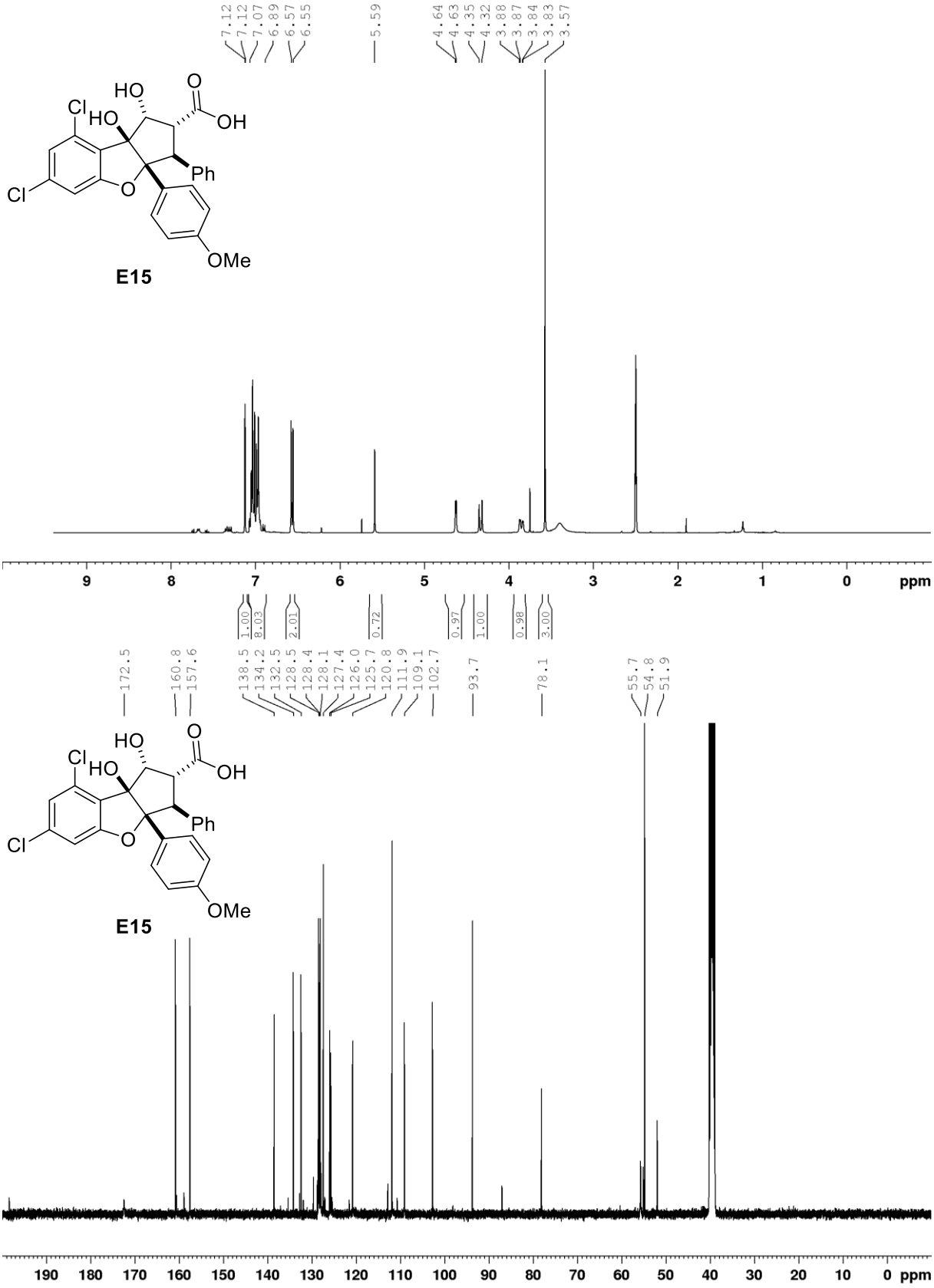
5,7-Dichloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (141)



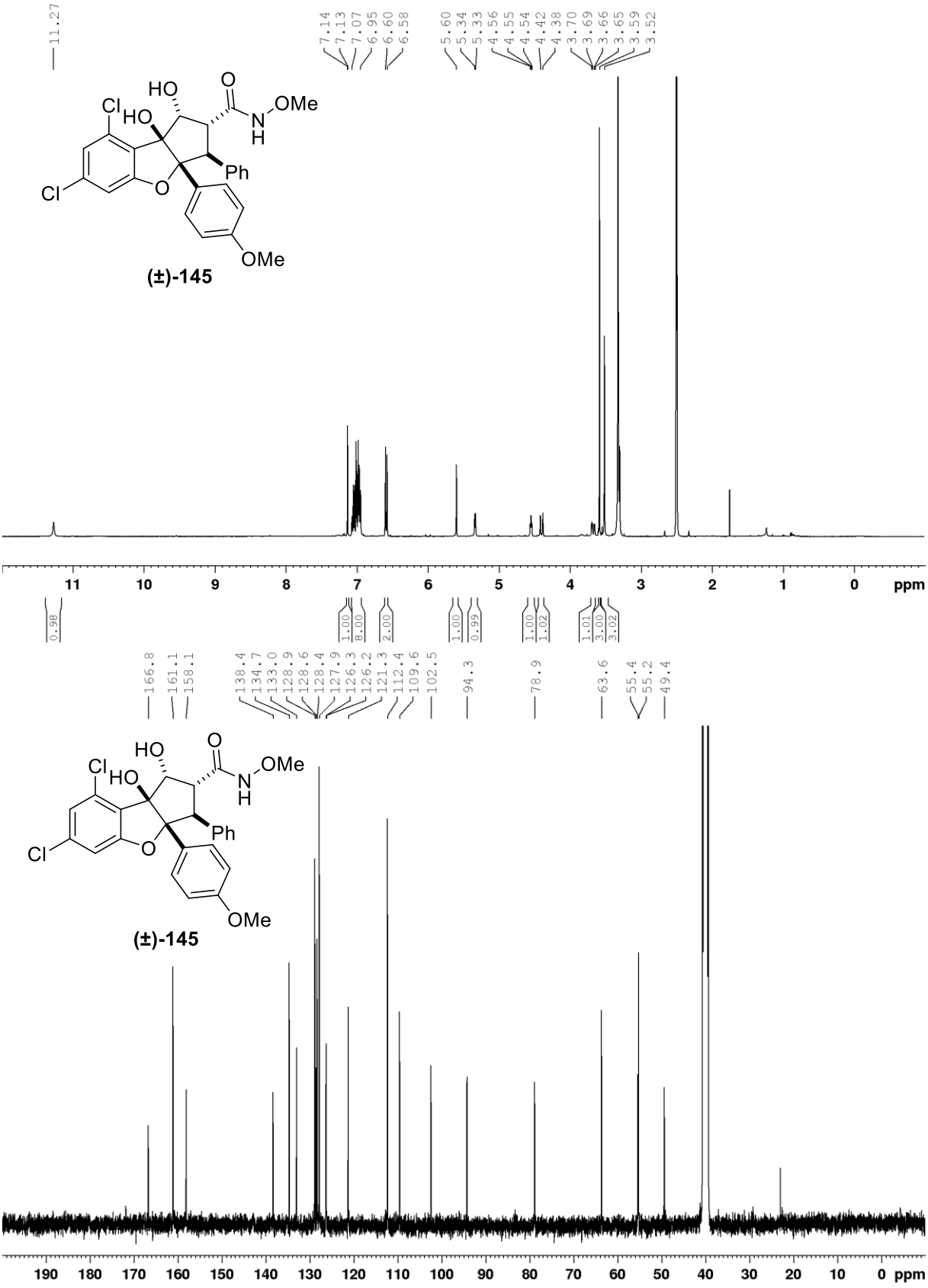
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-dichloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-143)



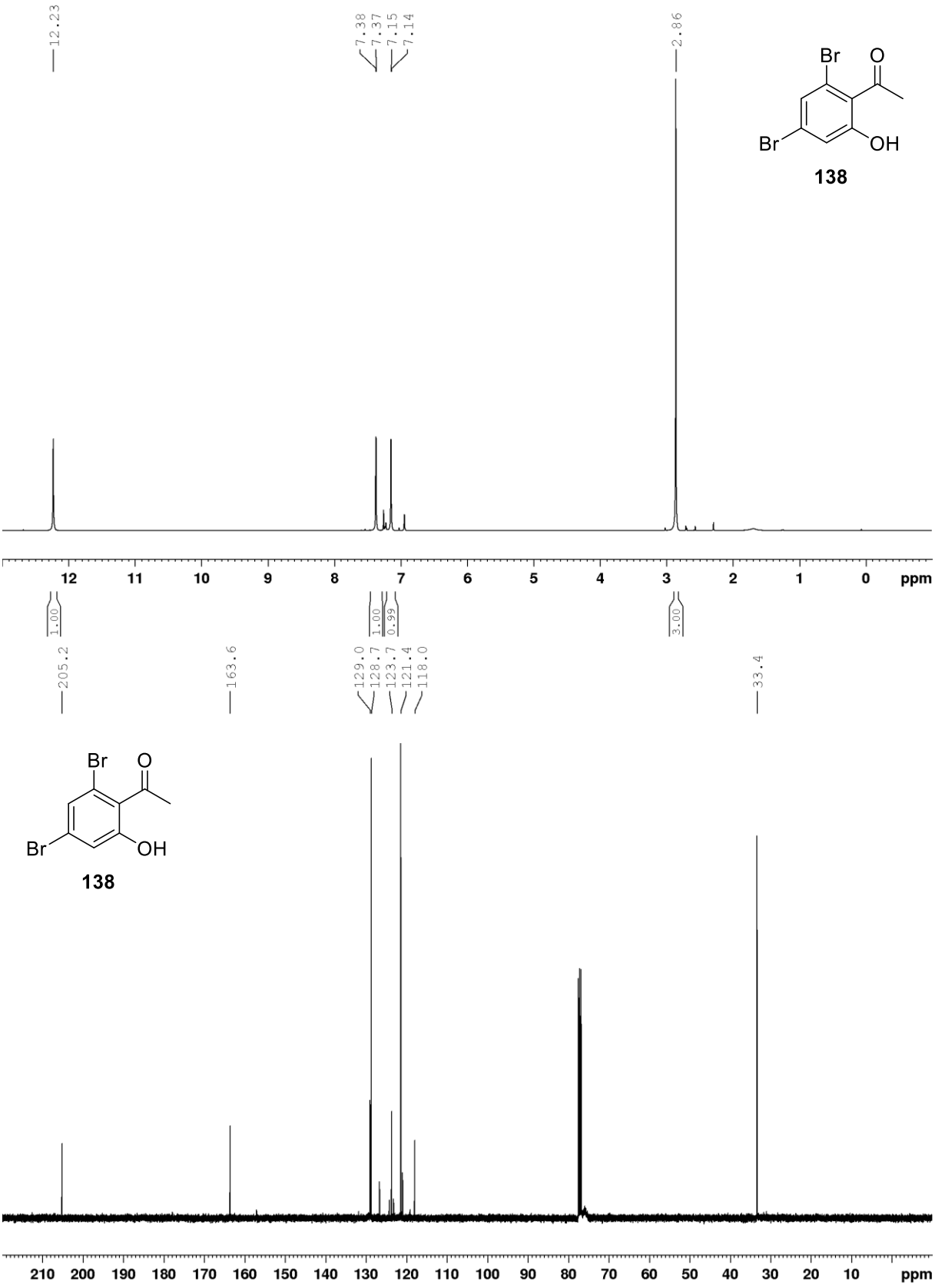
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-Dichloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (E15)



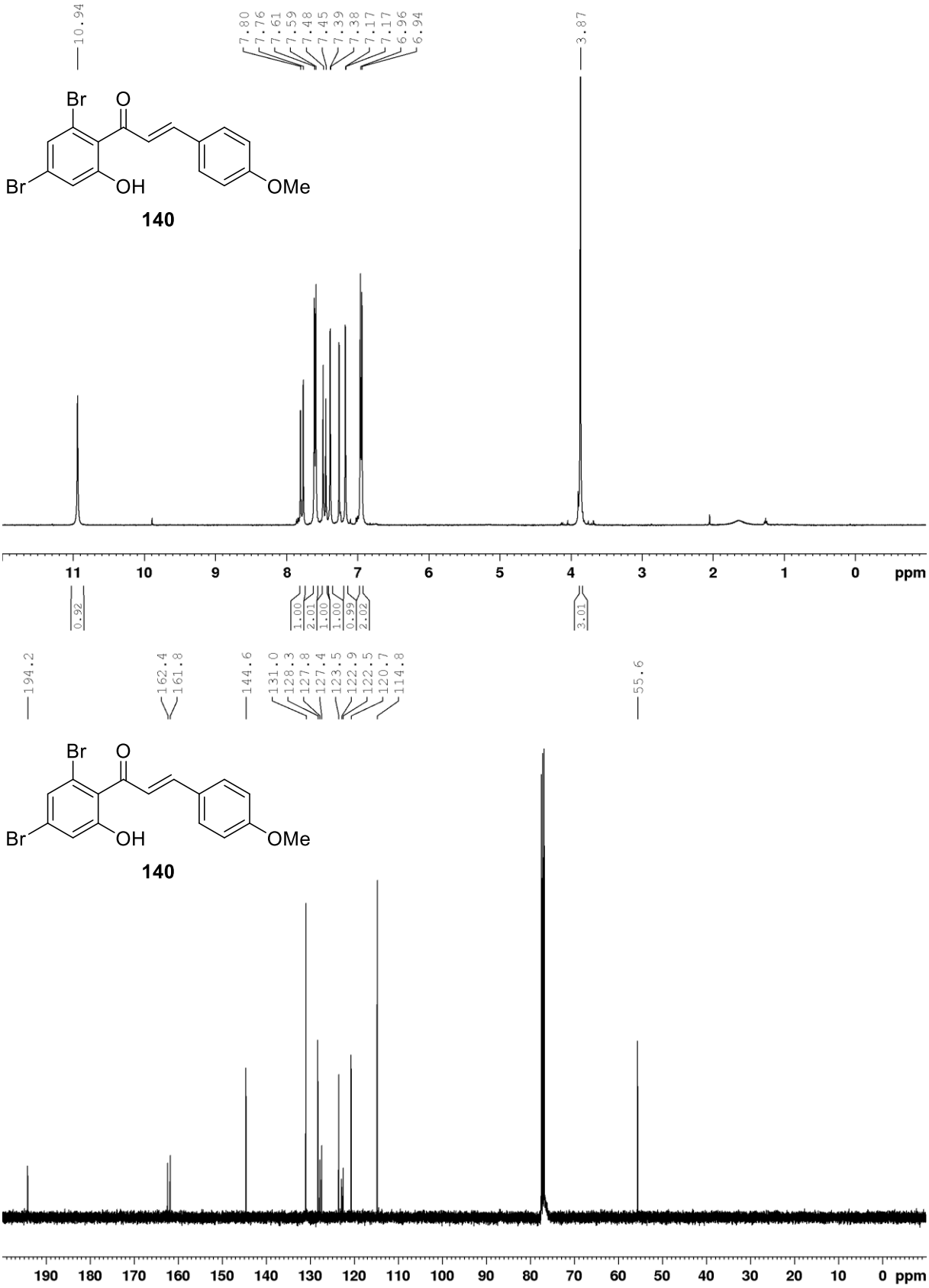
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-Dichloro-1,8b-dihydroxy-*N*-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-145)



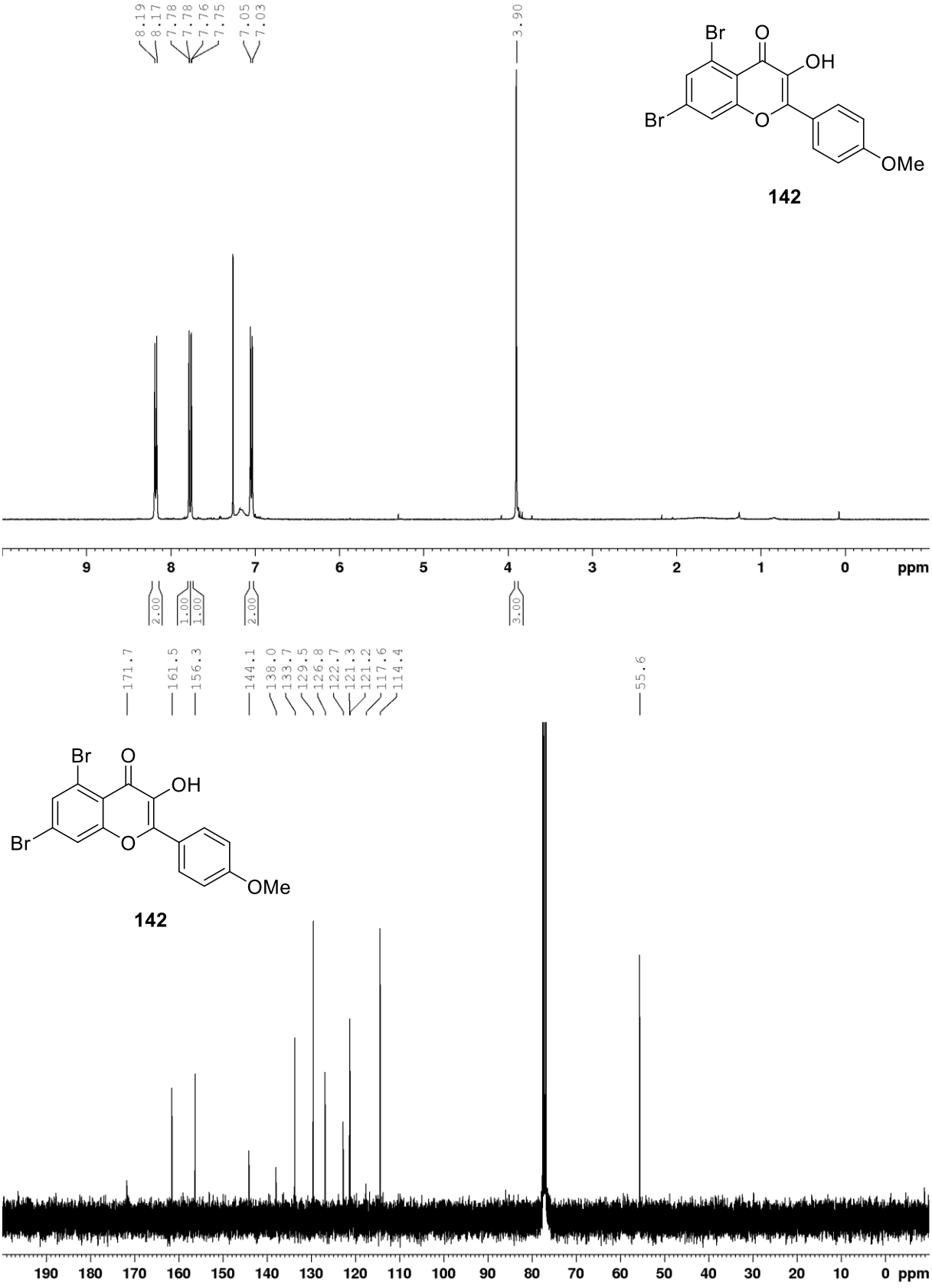
1-(2,4-Bromo-6-hydroxyphenyl)ethan-1-one (138)



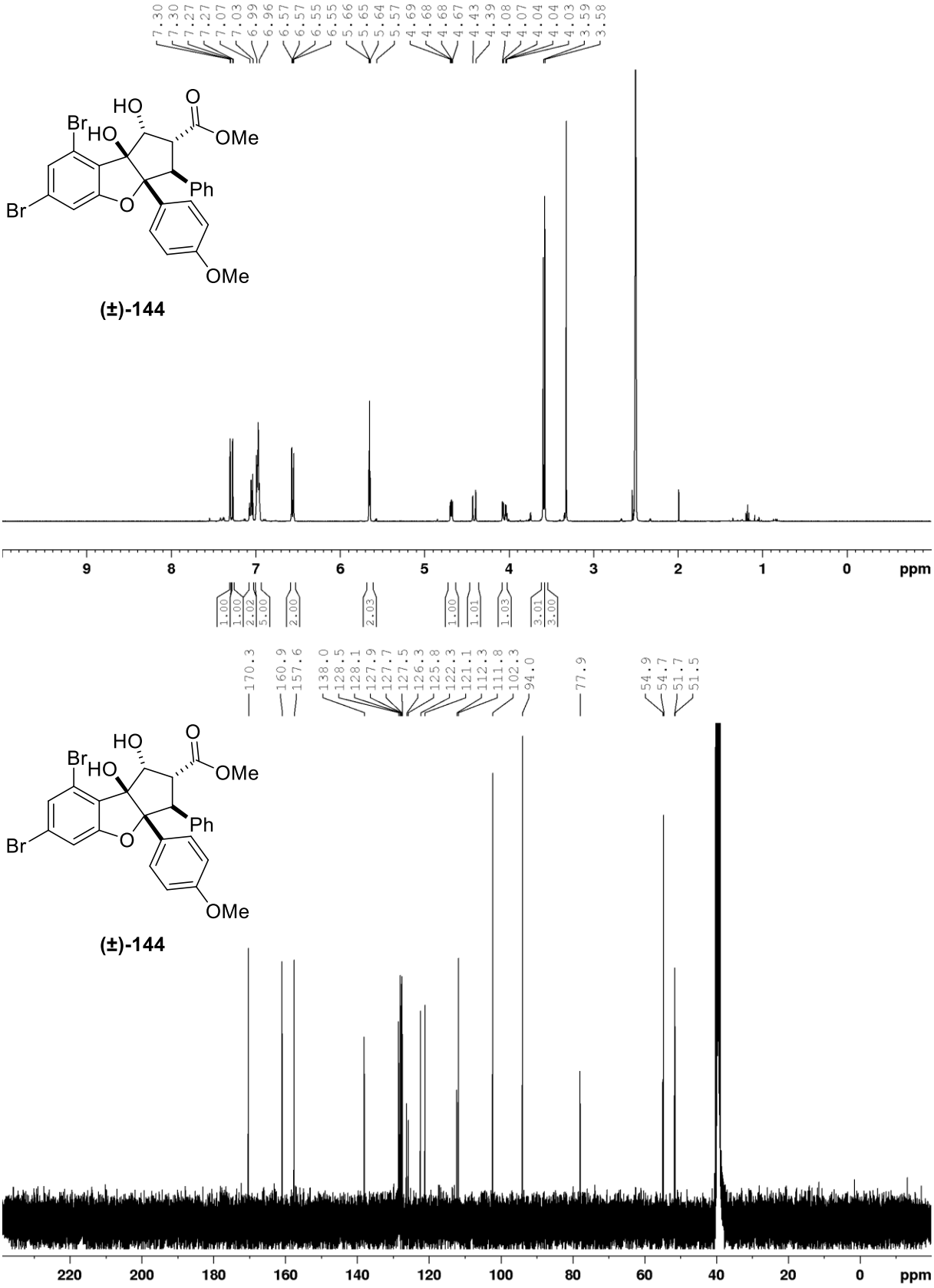
(*E*)-1-(2,4-Dibromo-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (140)



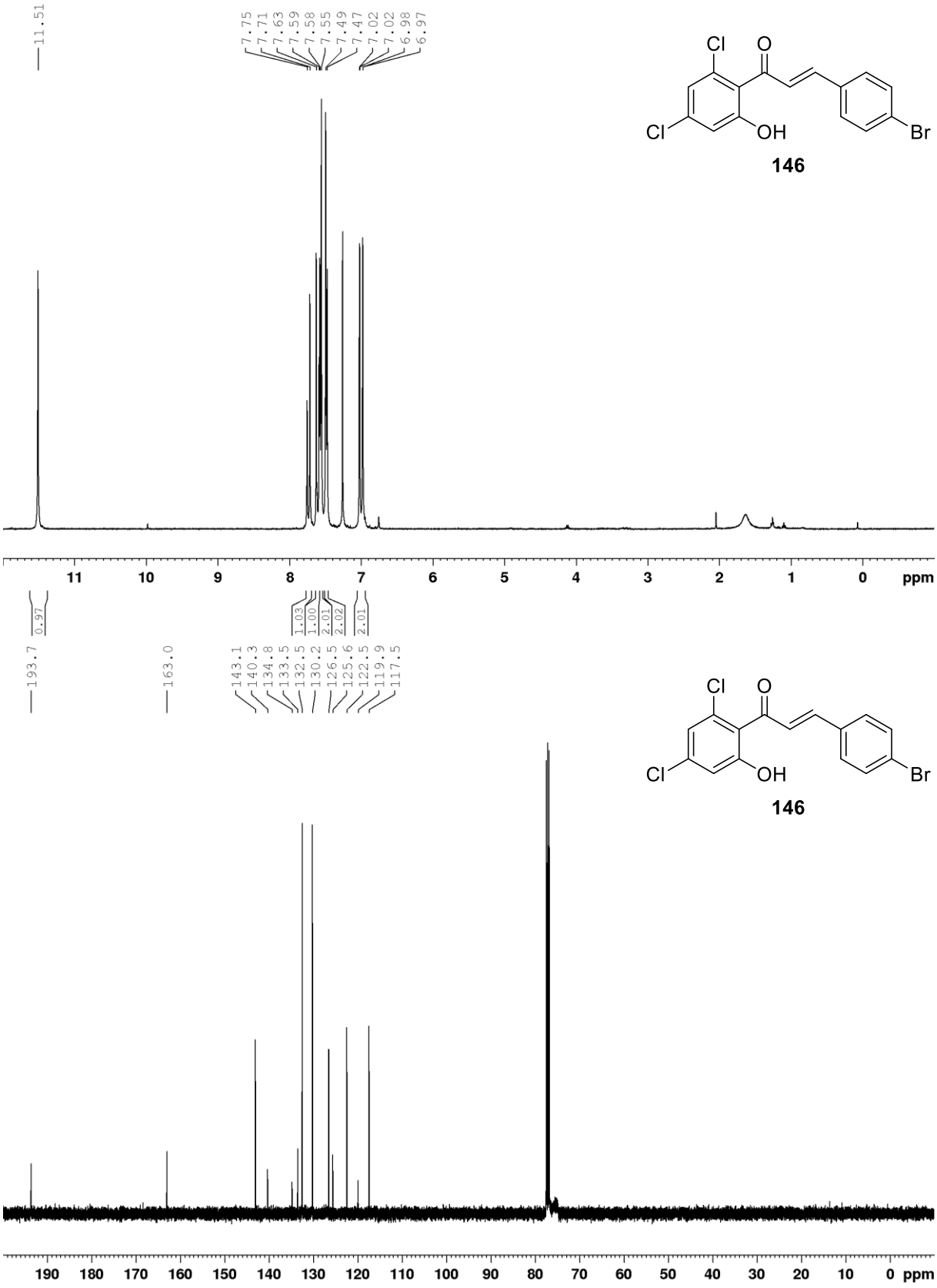
5,7-Dibromo-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (142)



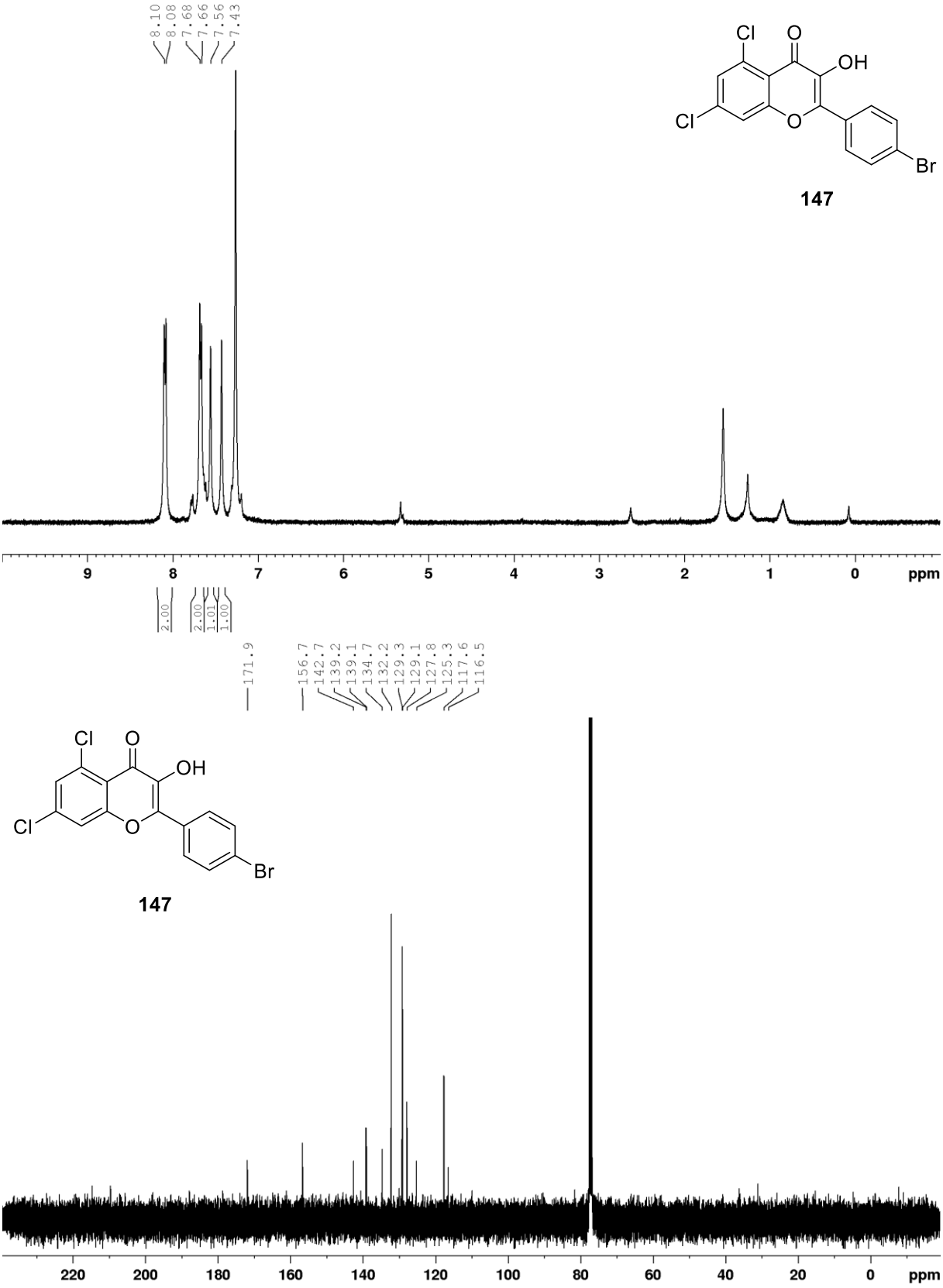
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6,8-dibromo-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-144)



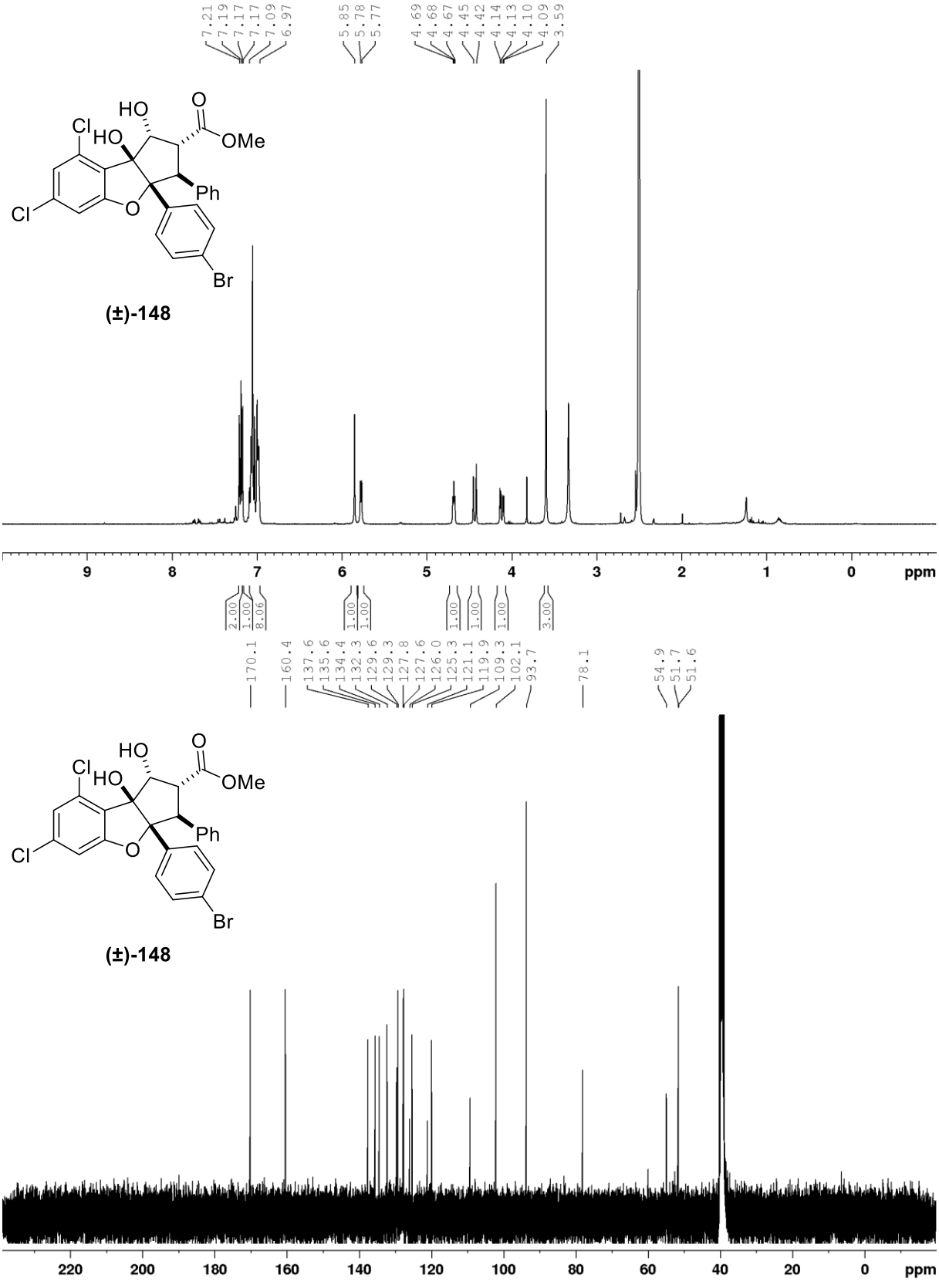
(*E*)-3-(4-Bromophenyl)-1-(2,4-dichloro-6-hydroxyphenyl)prop-2-en-1-one (146)



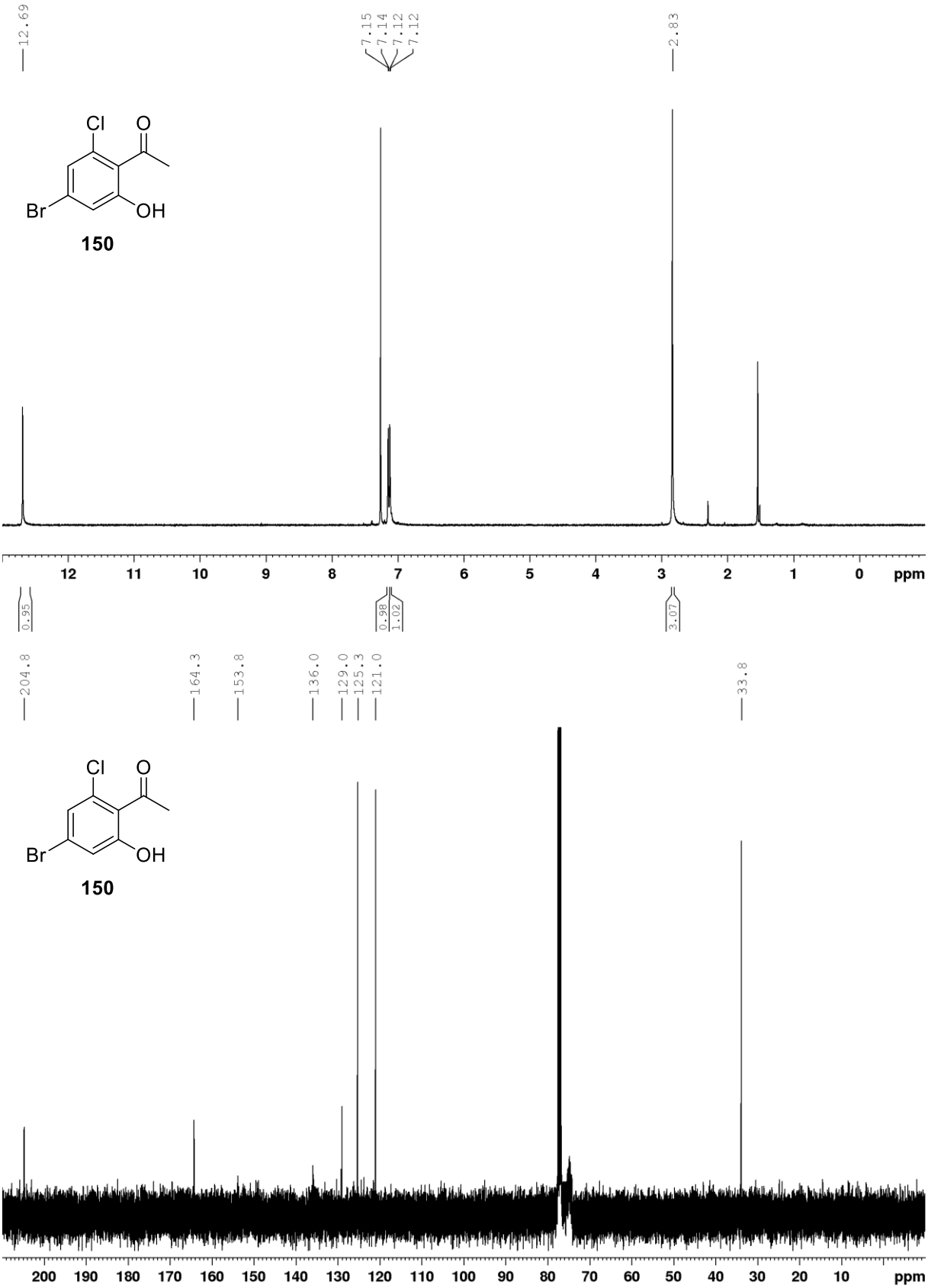
2-(4-Bromophenyl)-5,7-dichloro-3-hydroxy-4*H*-chromen-4-one (147)



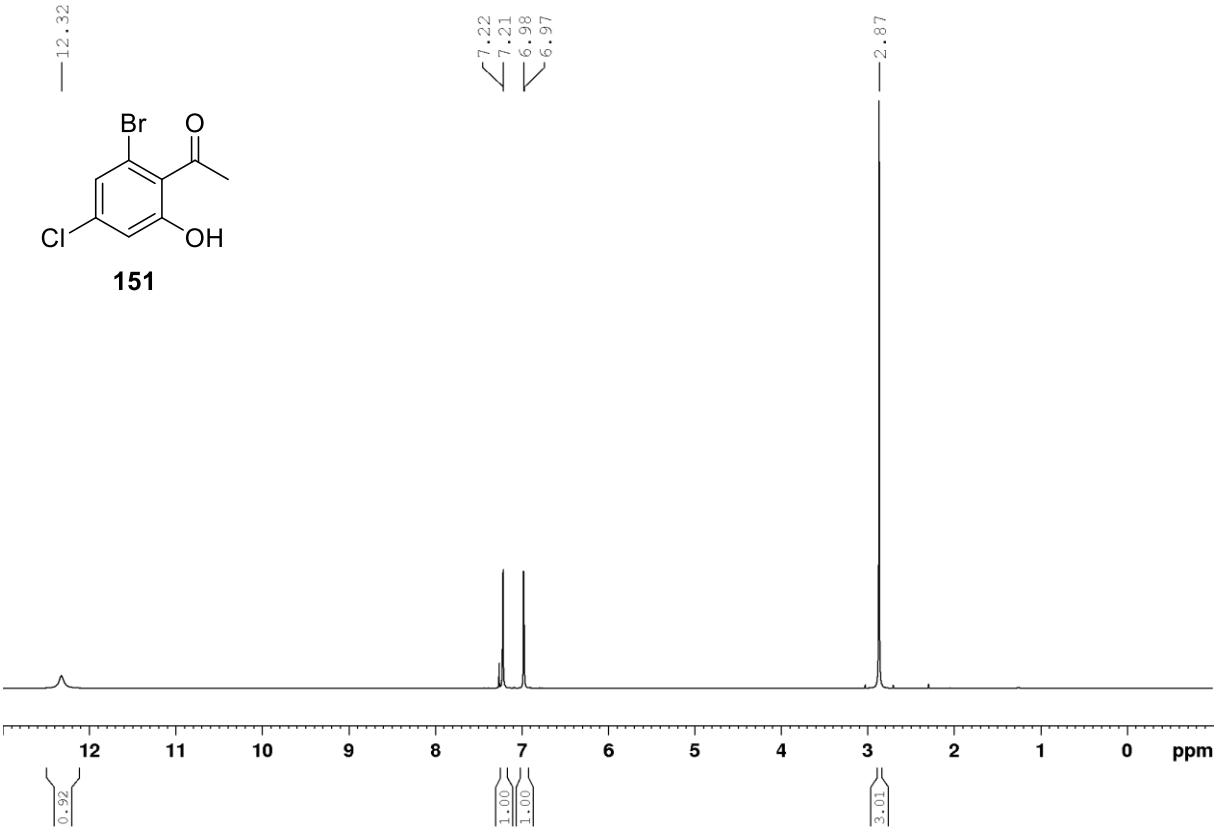
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6,8-dichloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-148)

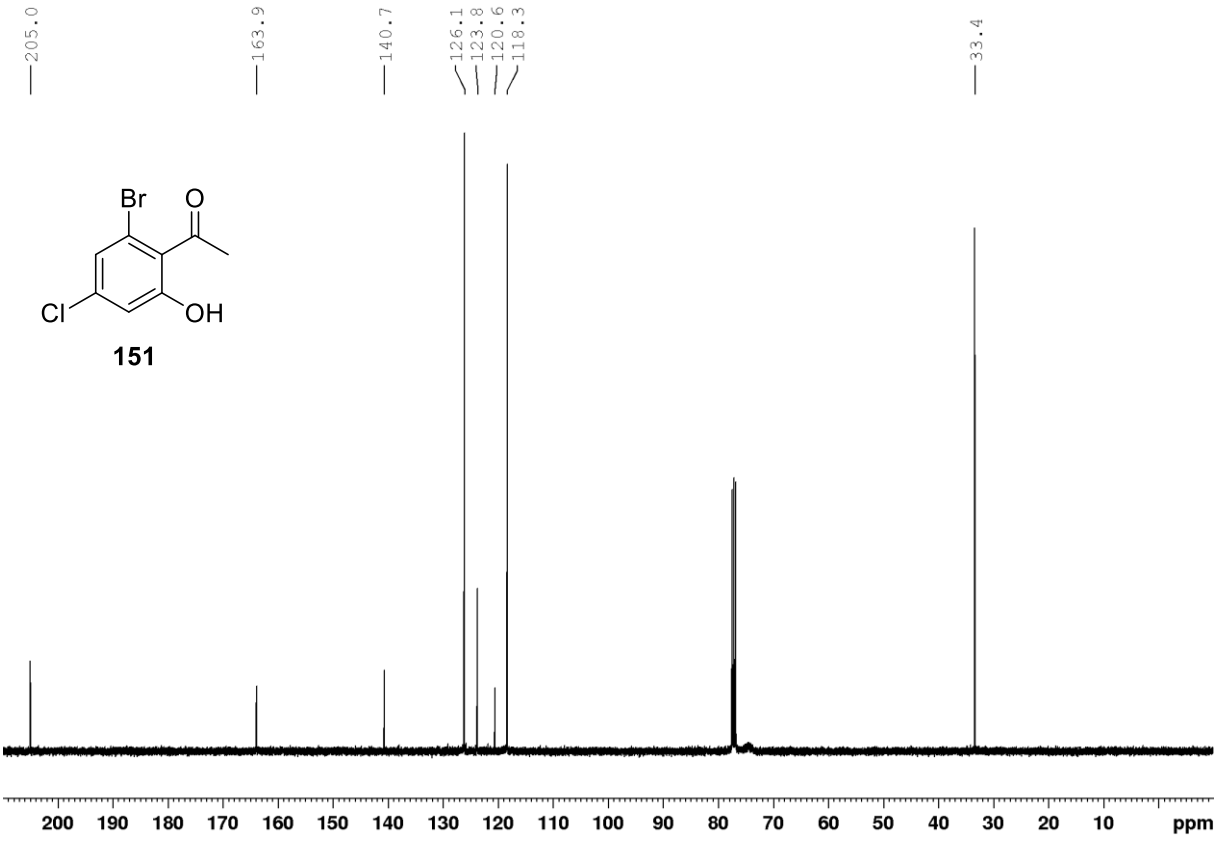


1-(4-Bromo-2-chloro-6-hydroxyphenyl)ethan-1-one (150)

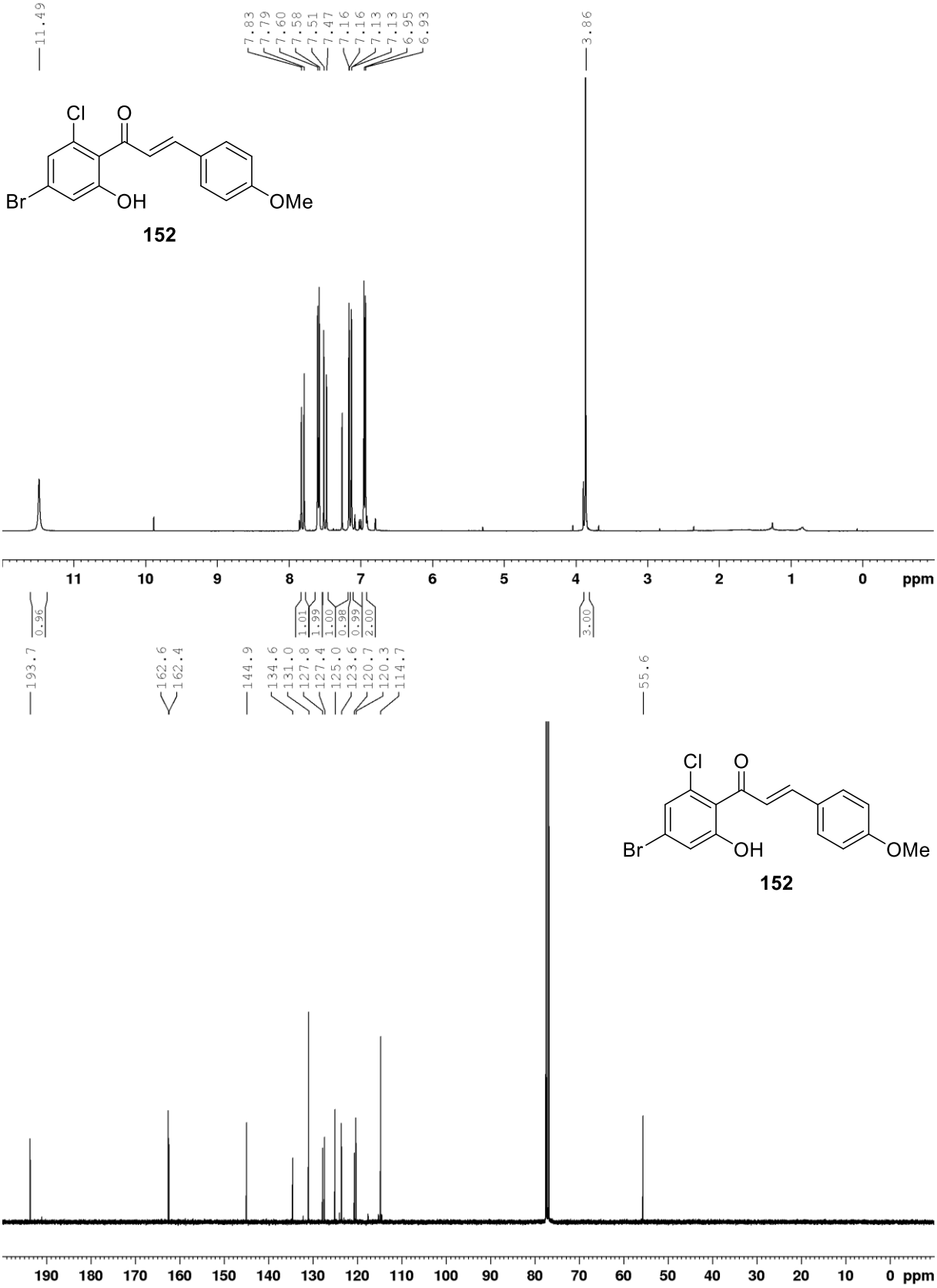


1-(2-Bromo-4-chloro-6-hydroxyphenyl)ethan-1-one (151)

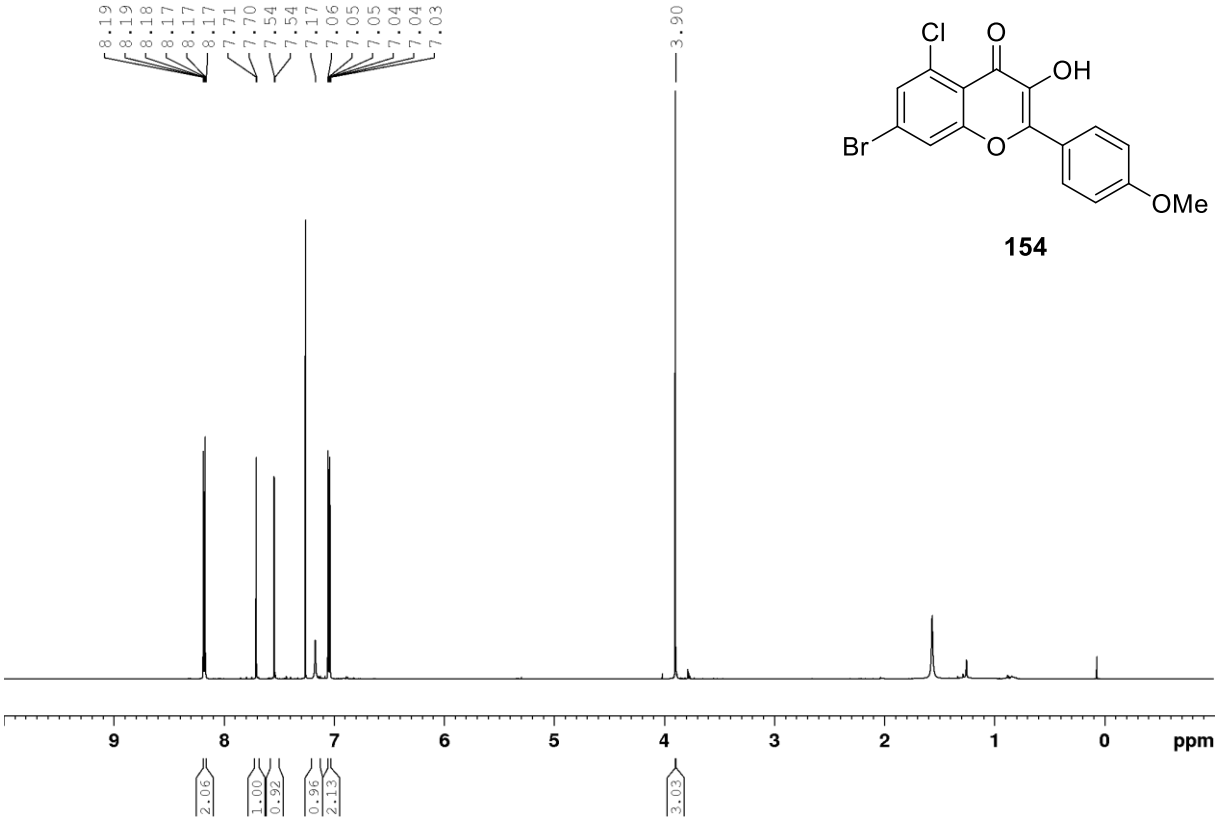


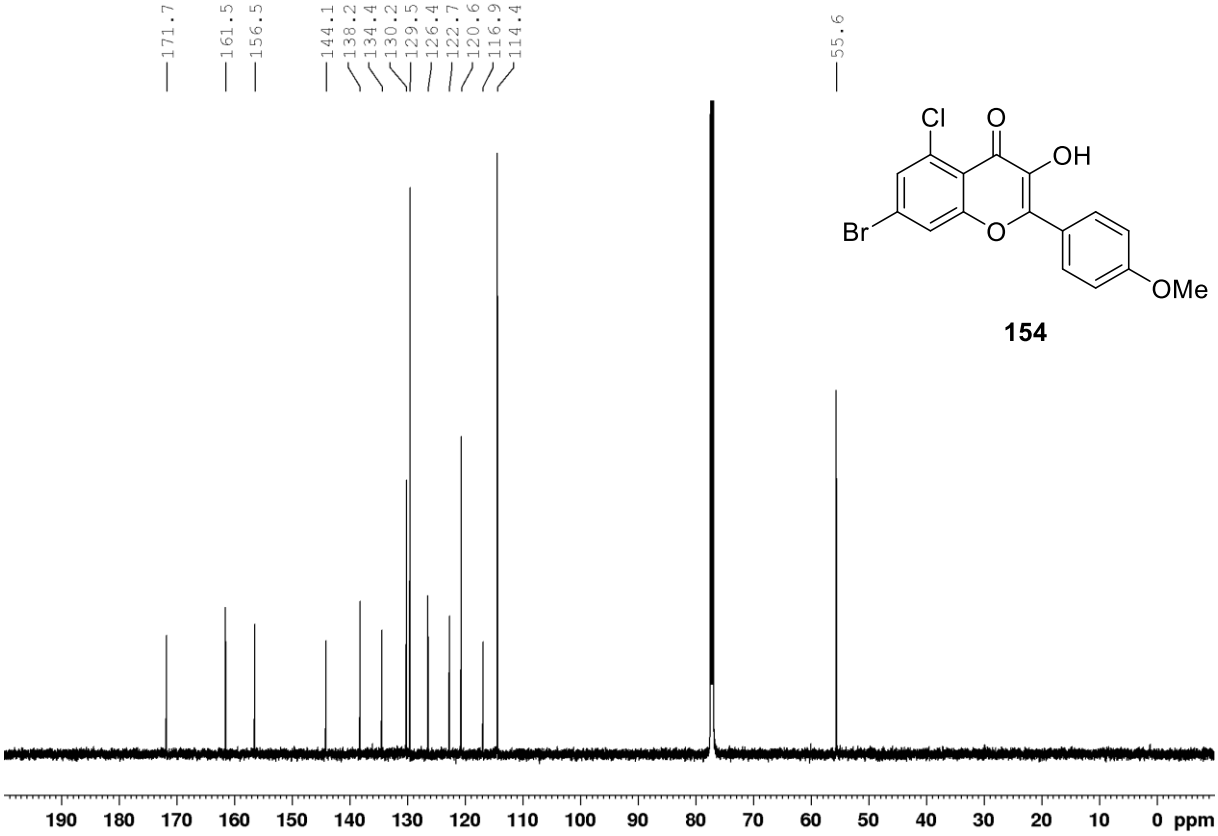


(*E*)-1-(4-Bromo-2-chloro-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (152)

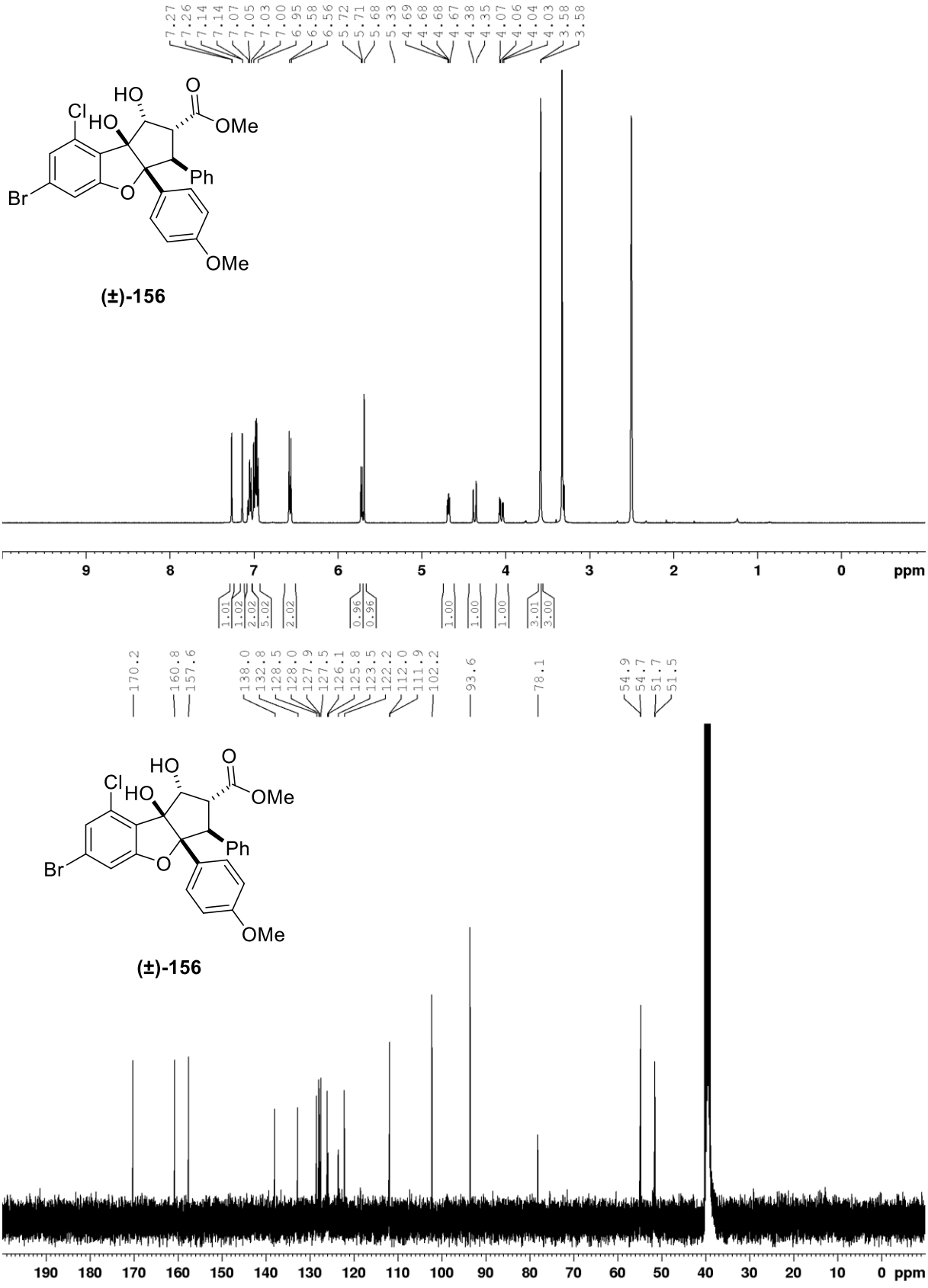


7-Bromo-5-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (154)

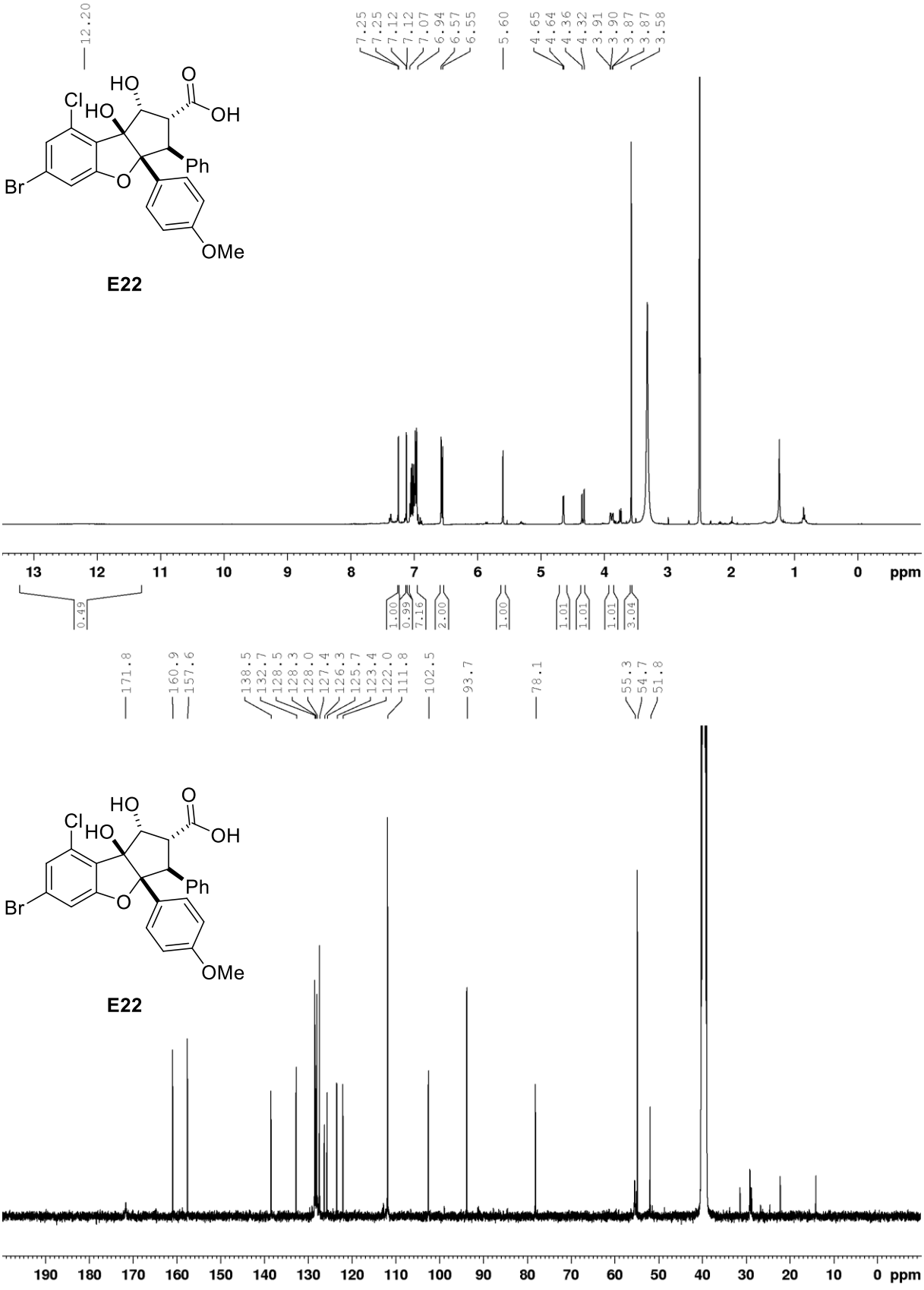




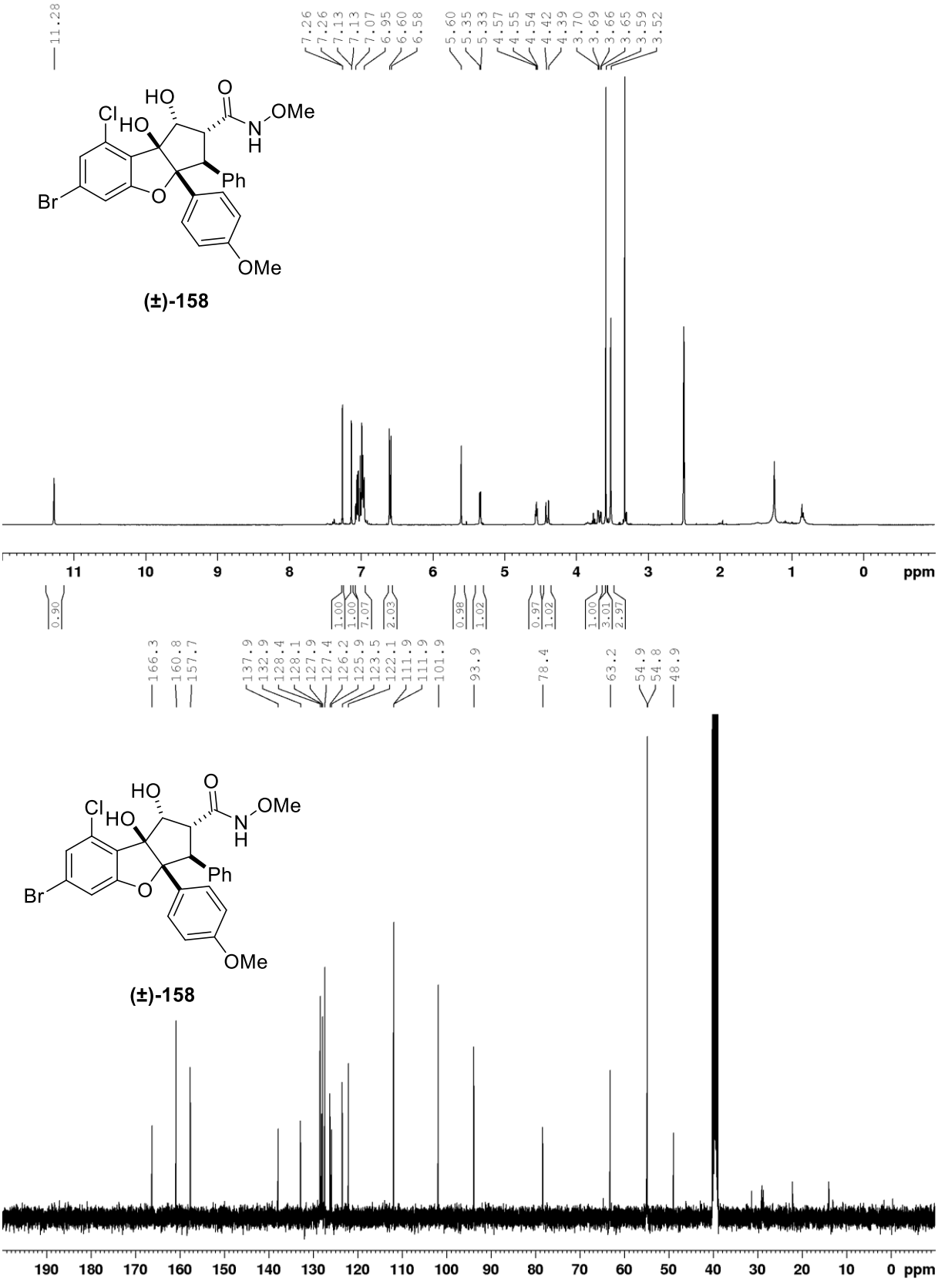
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-bromo-8-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-156)



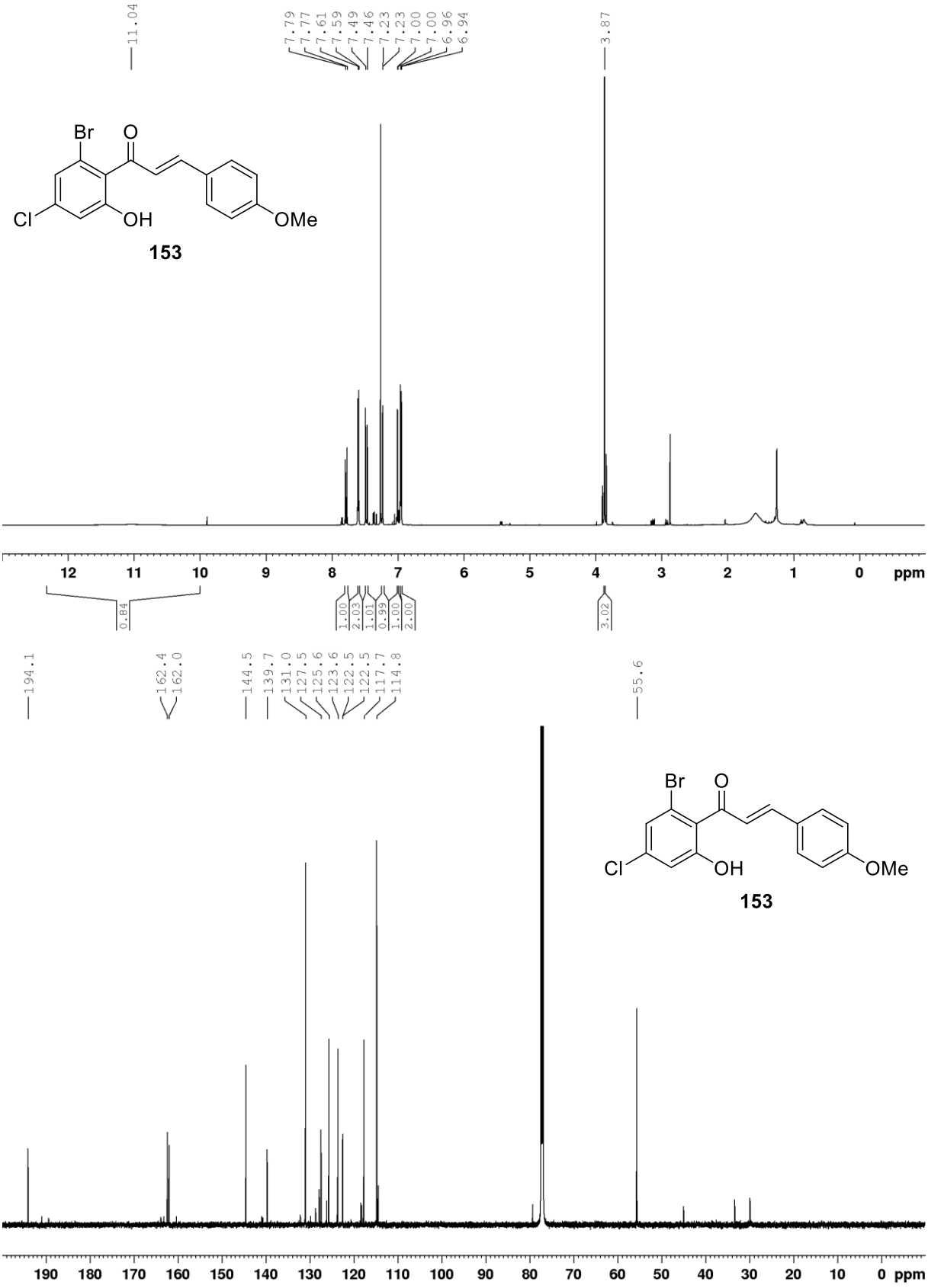
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-Bromo-8-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (E22)



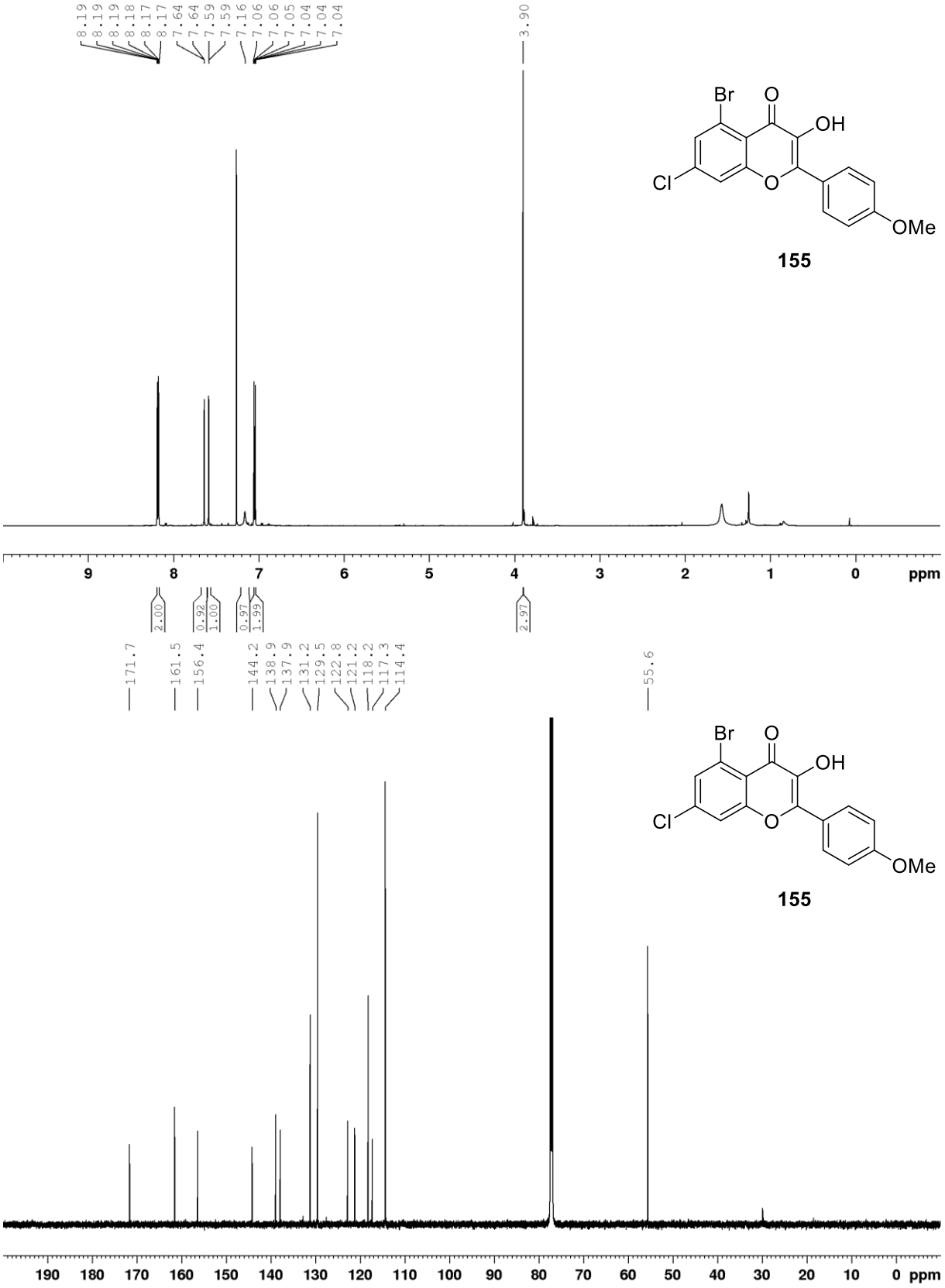
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-Bromo-8-chloro-1,8b-dihydroxy-*N*-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-158)



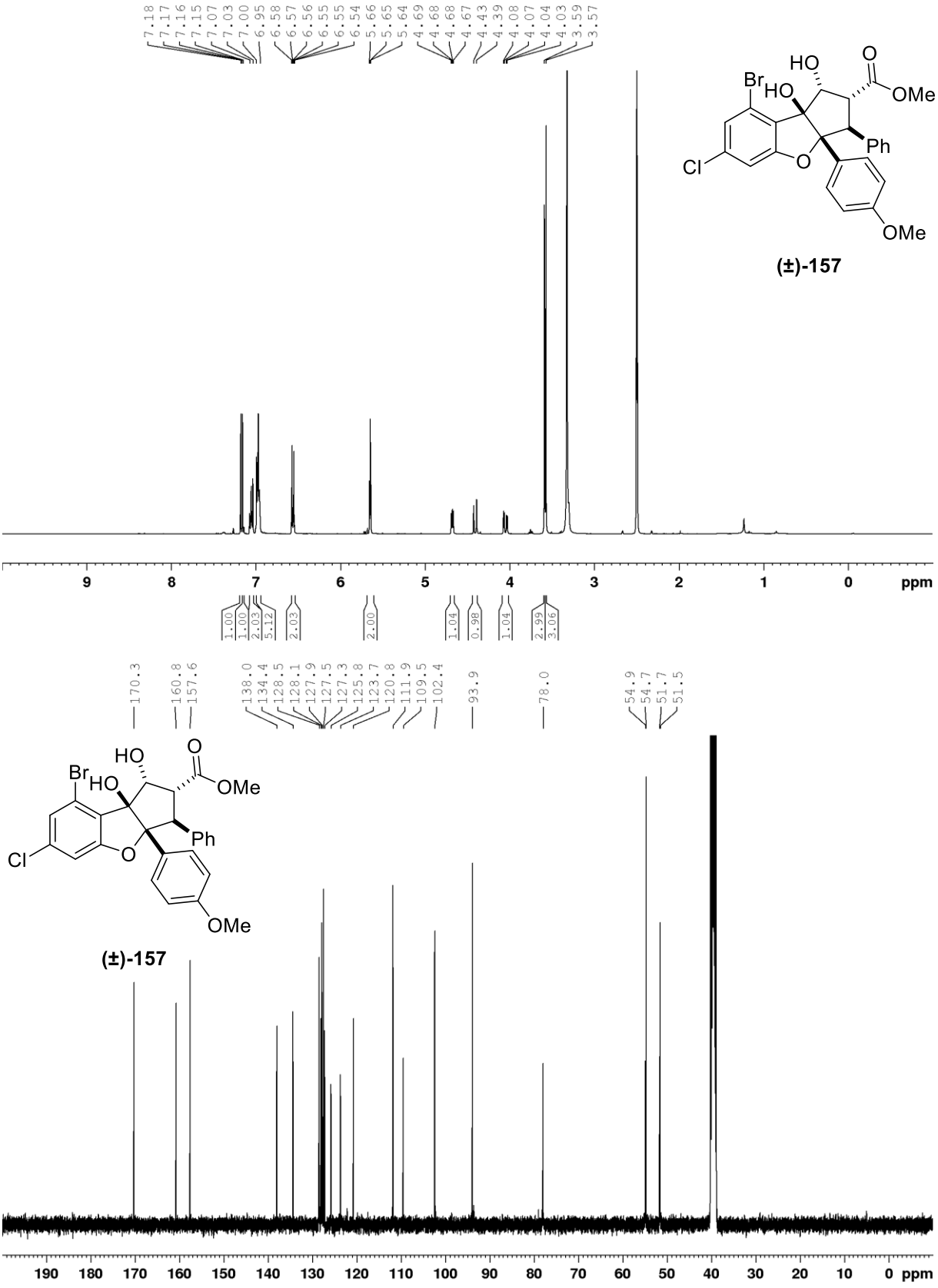
(*E*)-1-(2-Bromo-4-chloro-6-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (153)



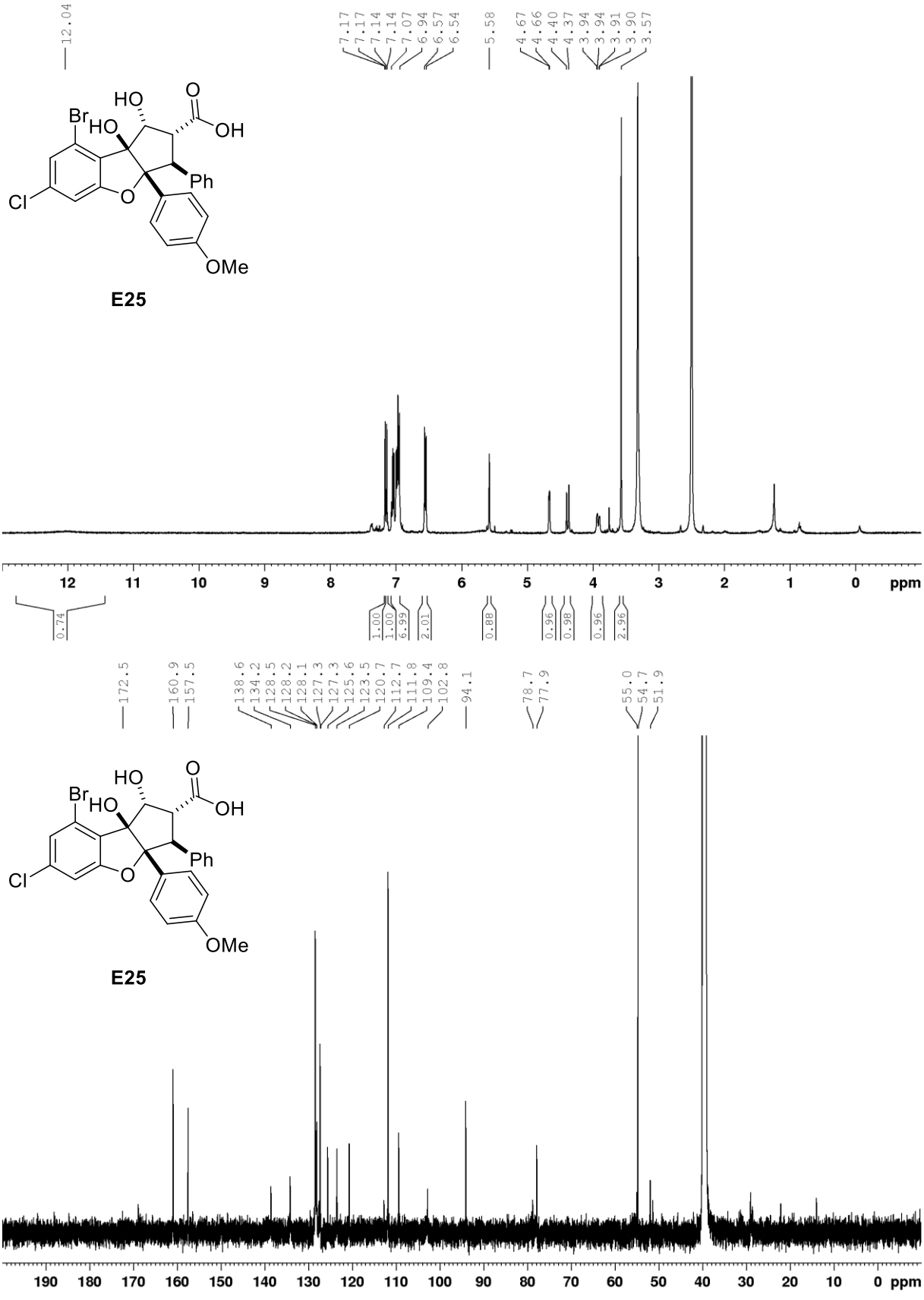
5-Bromo-7-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (155)



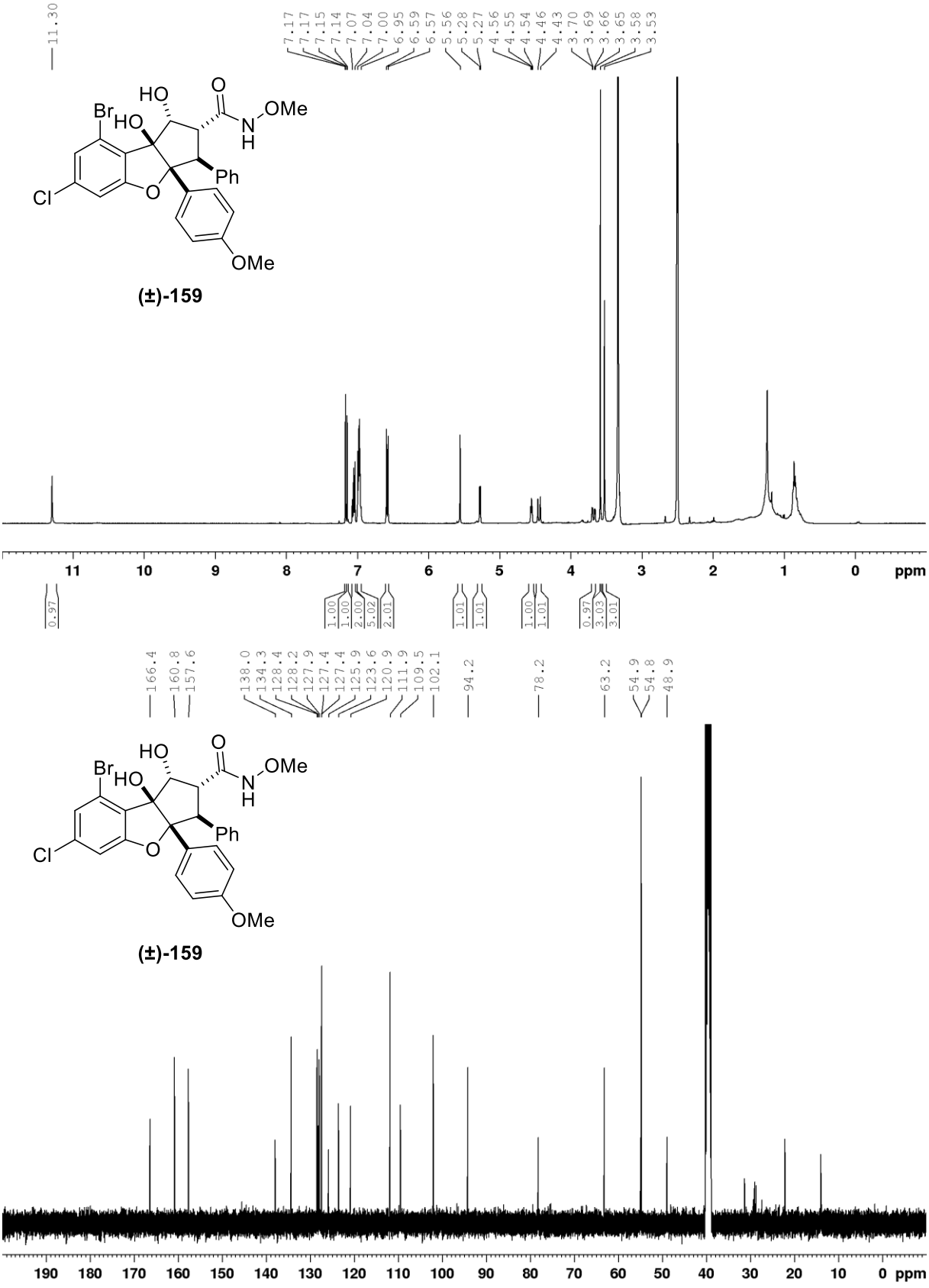
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-bromo-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-157)



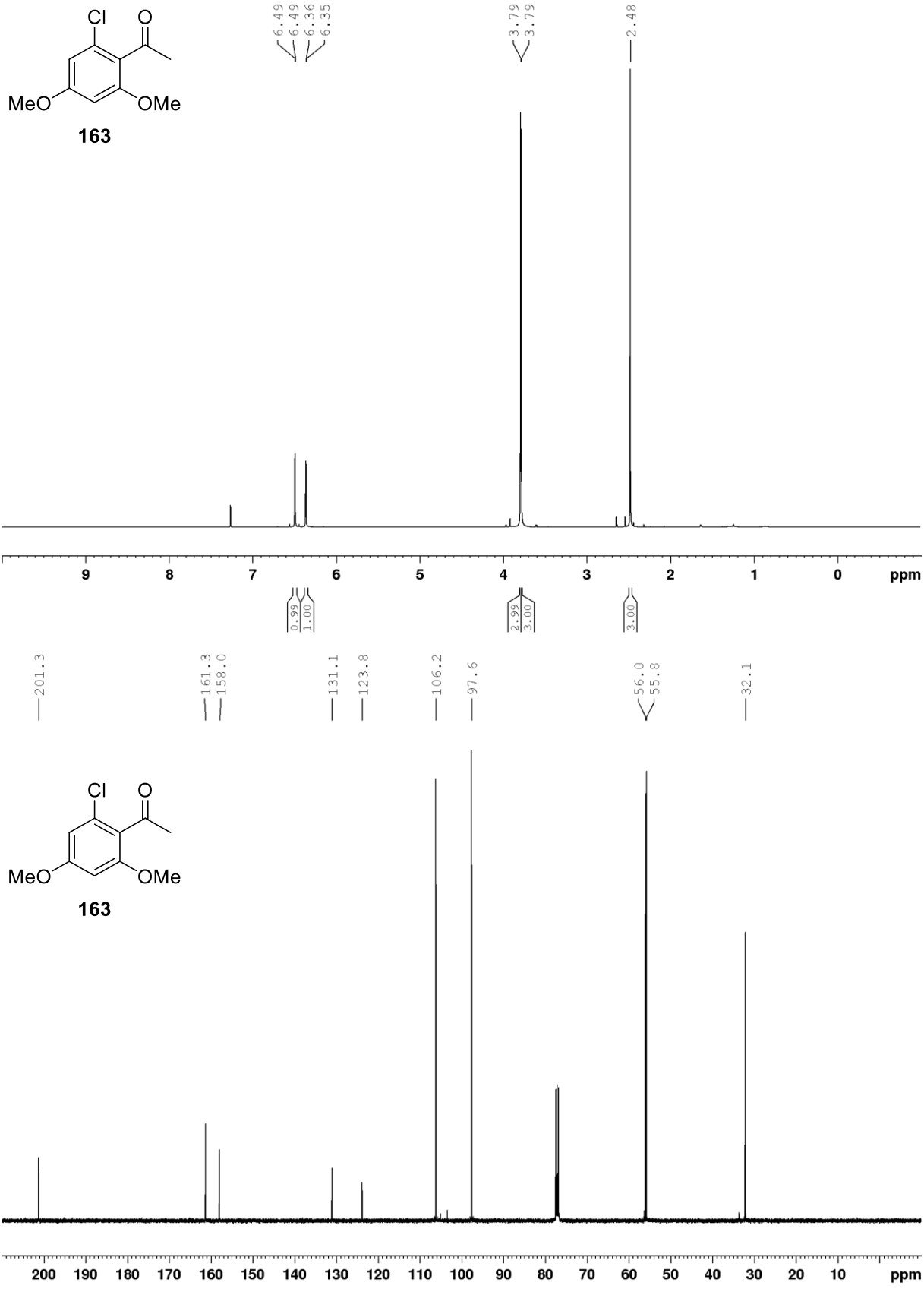
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-Bromo-8-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (E25)



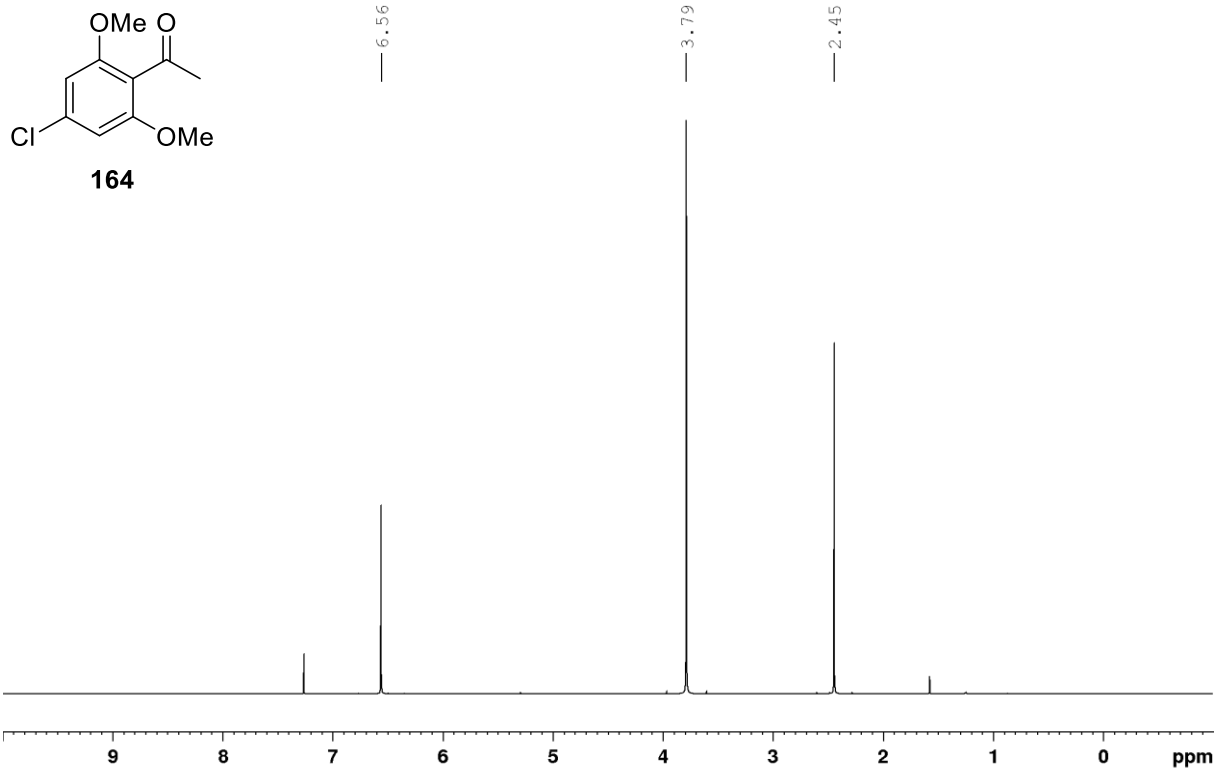
(±)-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-Bromo-6-chloro-1,8b-dihydroxy-*N*-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide ((±)-159)

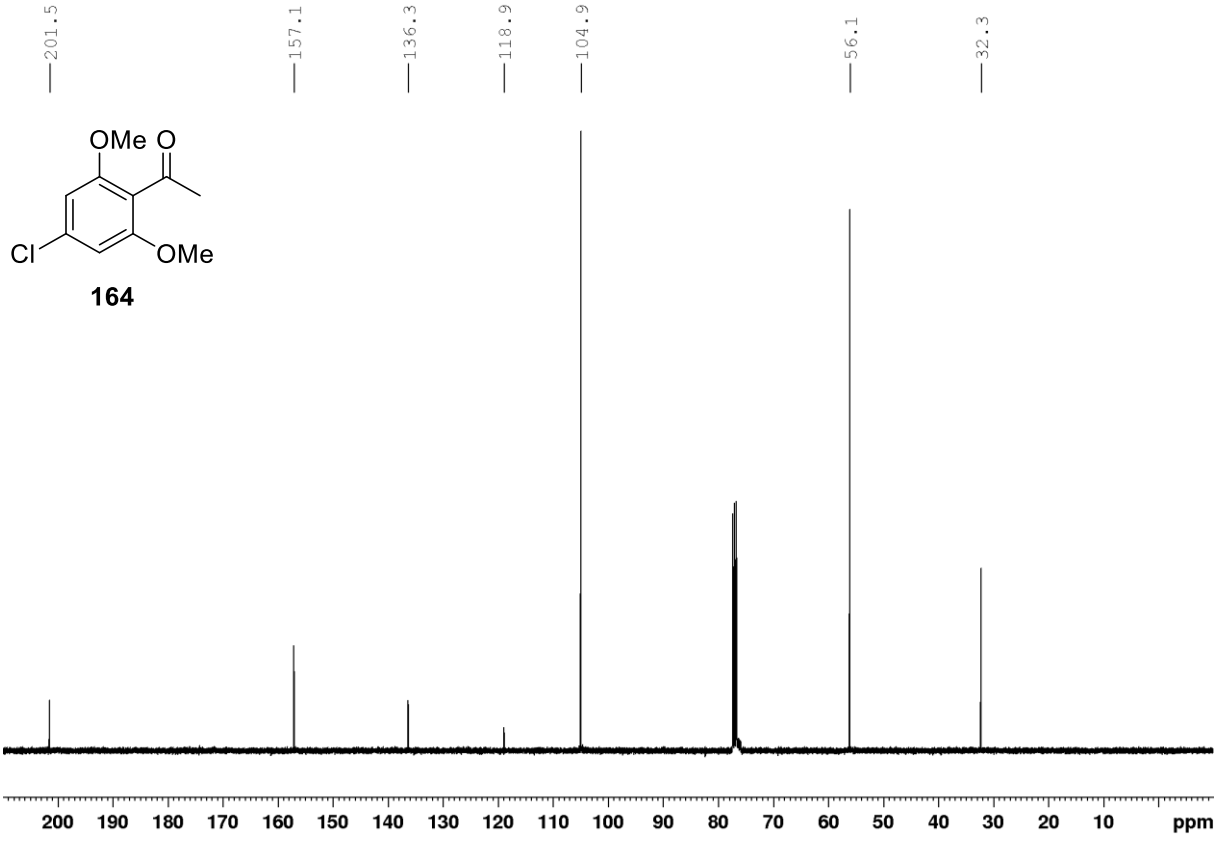


1-(2-Chloro-4,6-dimethoxyphenyl)ethan-1-one (163)

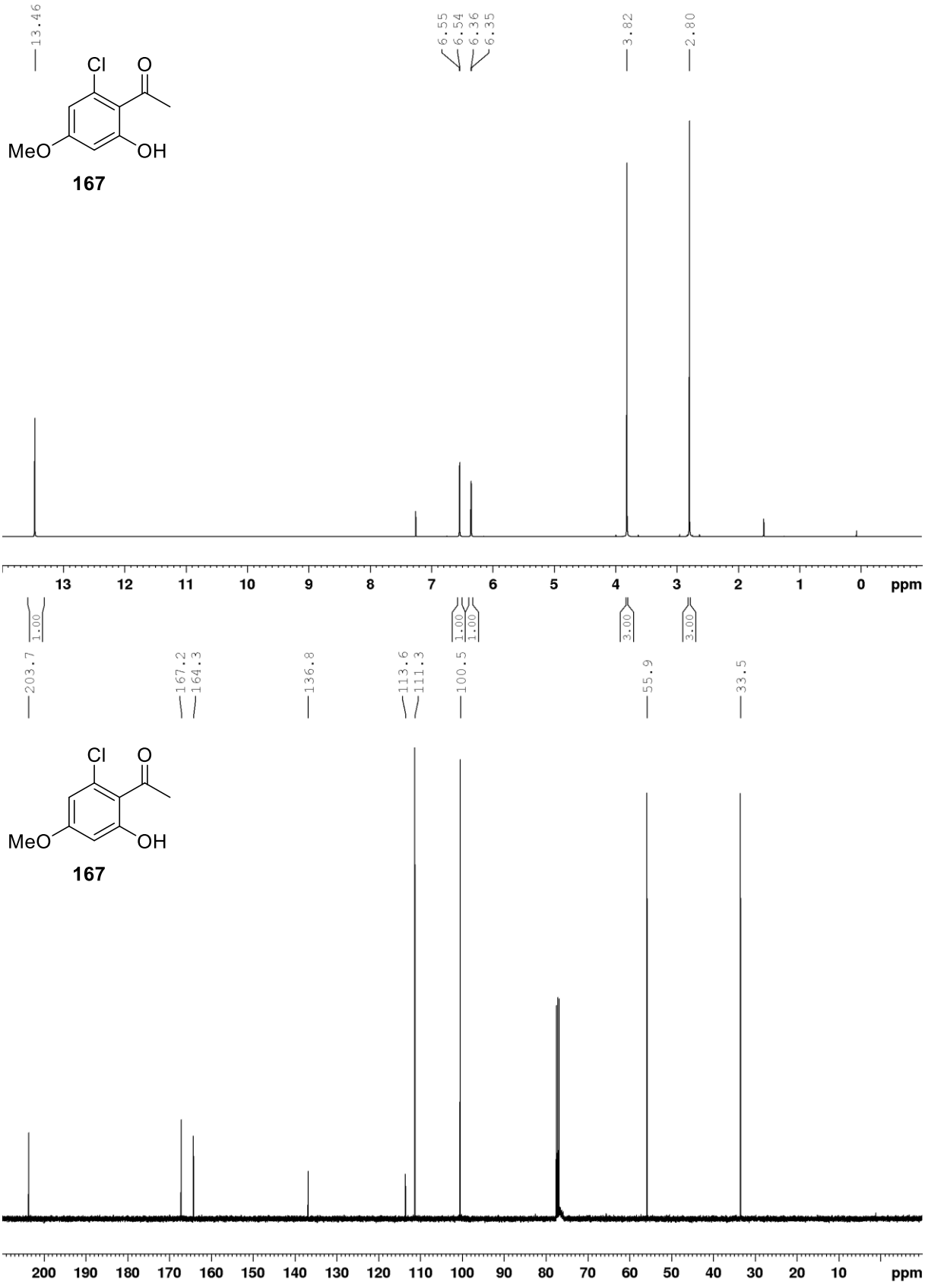


1-(4-Chloro-2,6-dimethoxyphenyl)ethan-1-one (164)

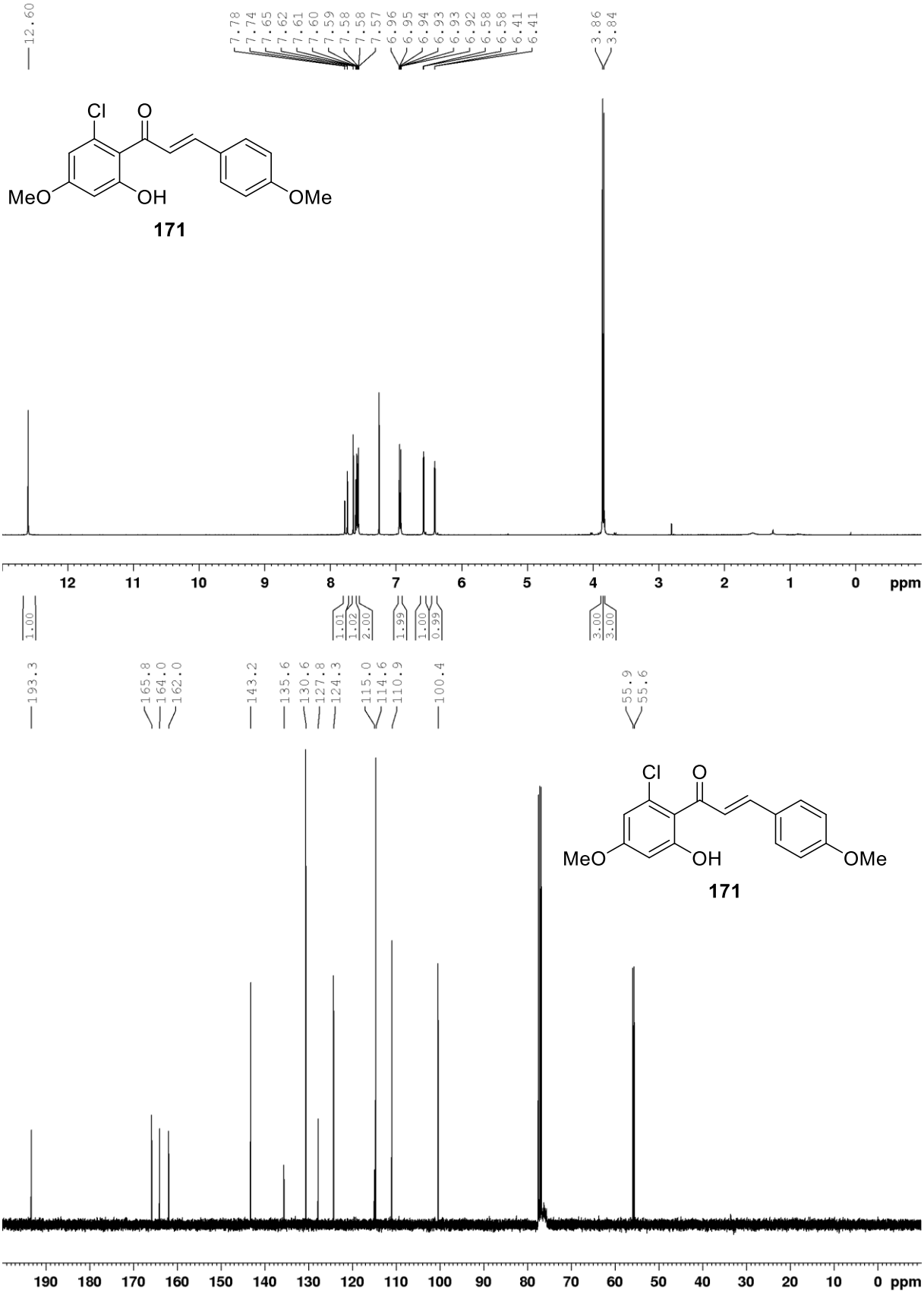




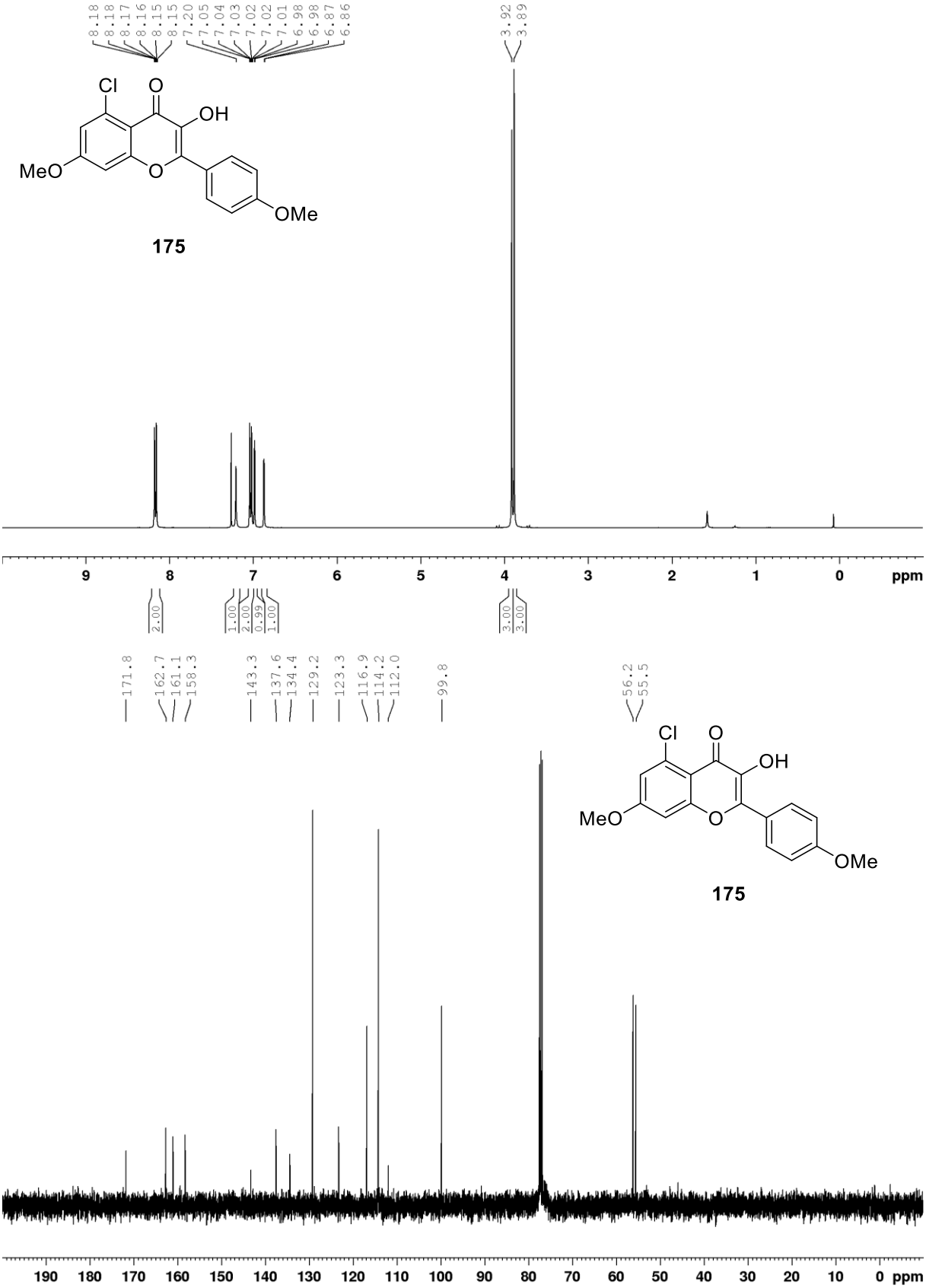
1-(2-Chloro-6-hydroxy-4-methoxyphenyl)ethan-1-one (167)



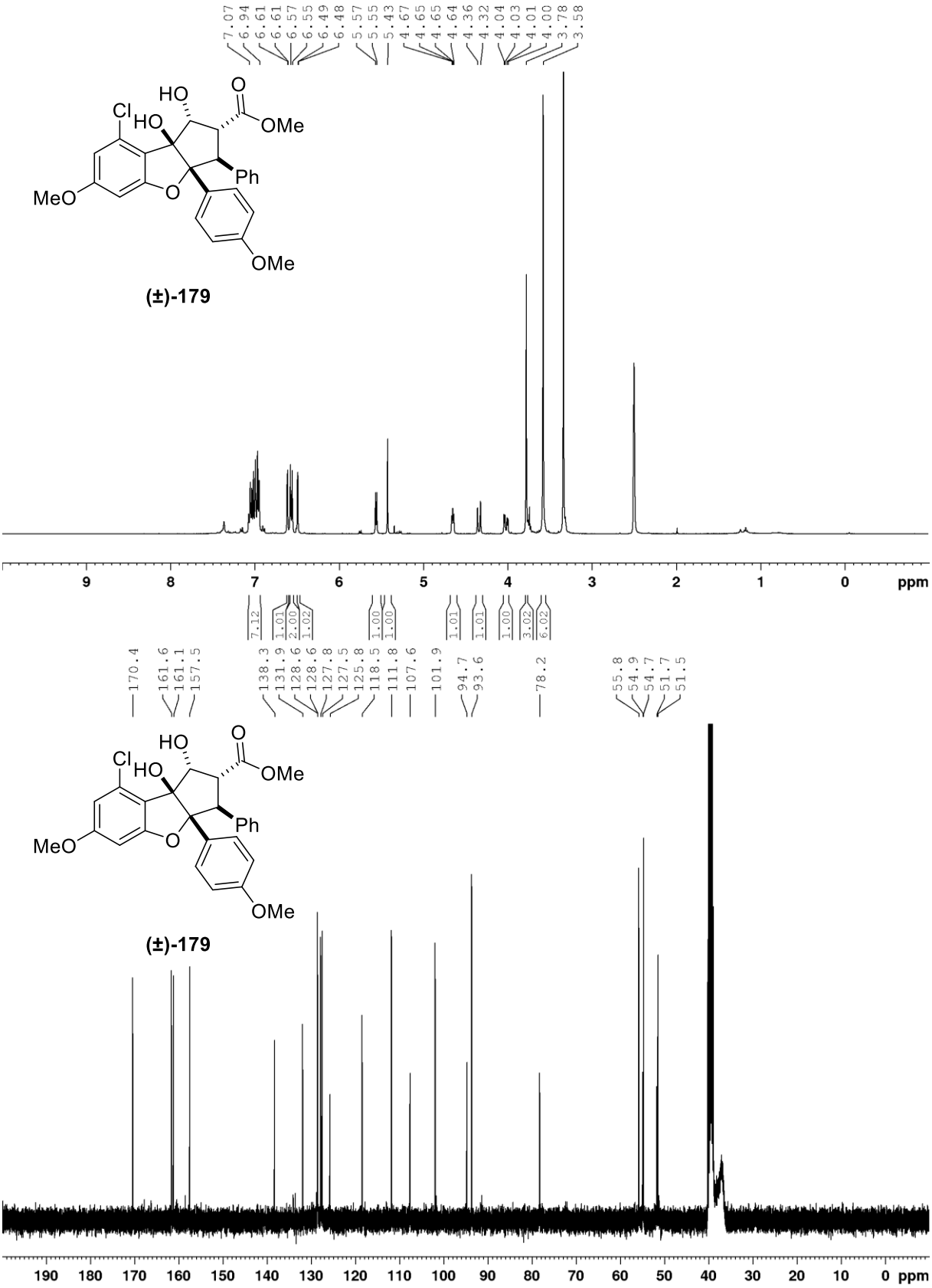
(*E*)-1-(2-Chloro-6-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (171)



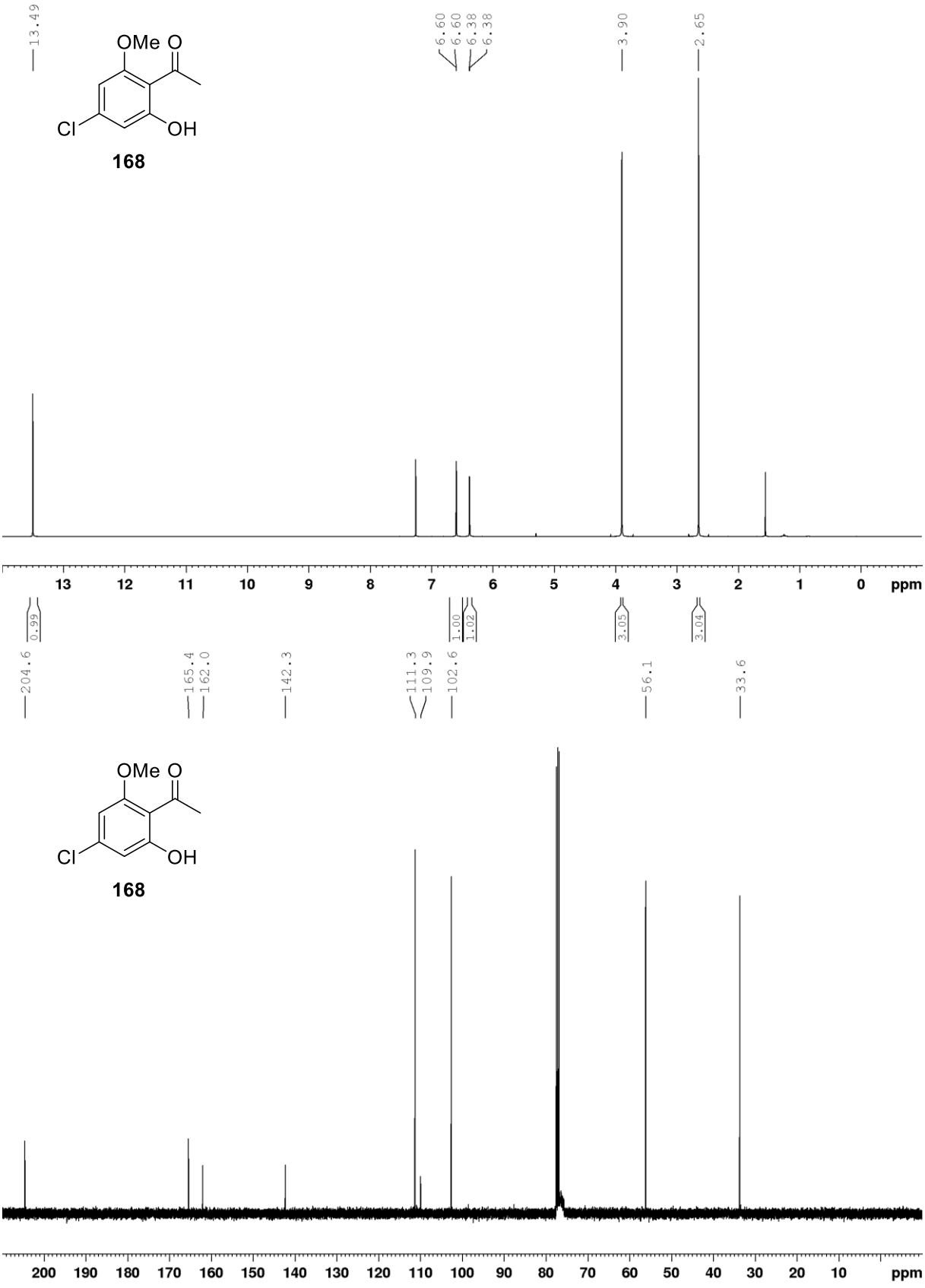
5-Chloro-3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (175)



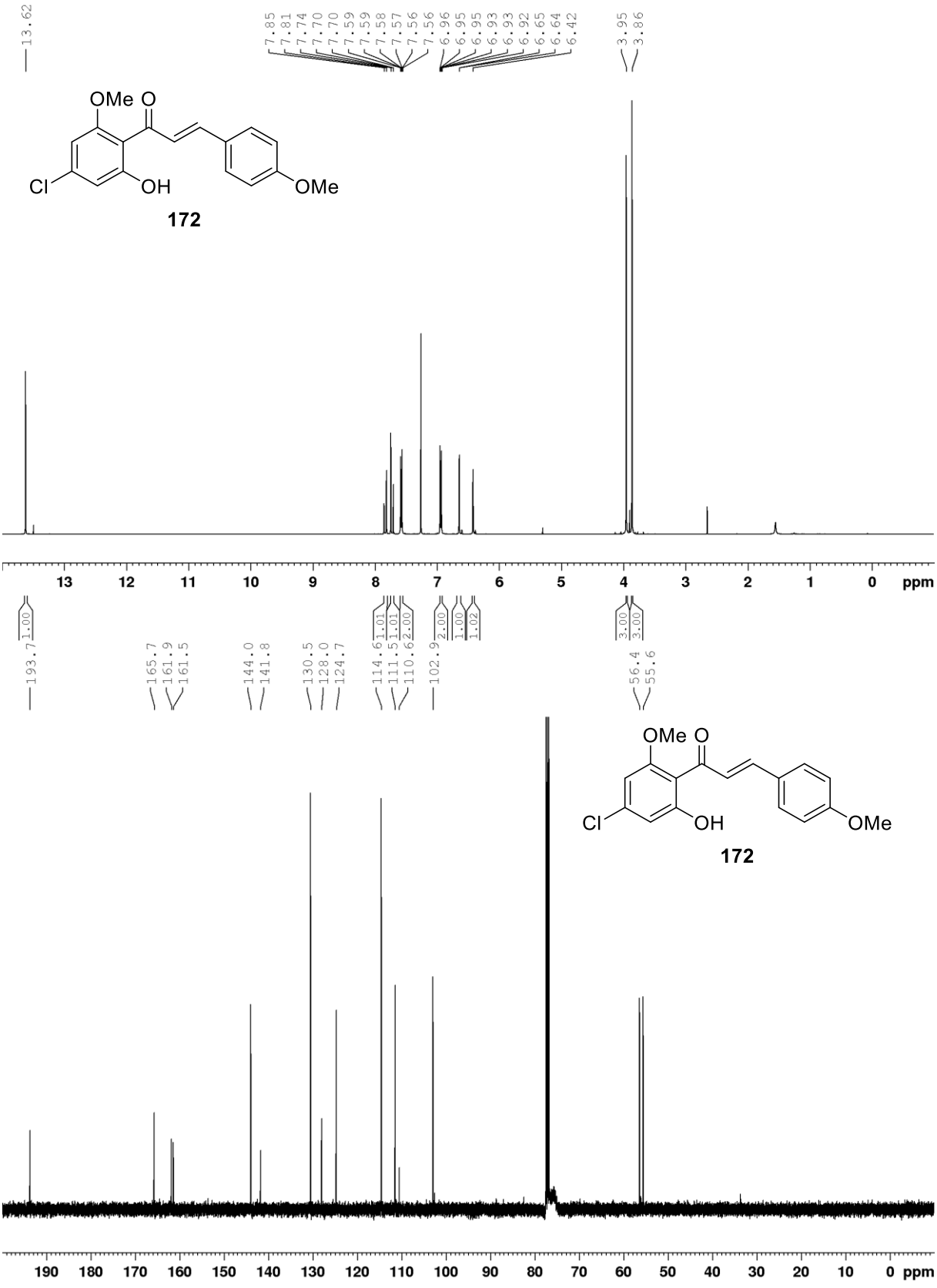
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-chloro-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-179)



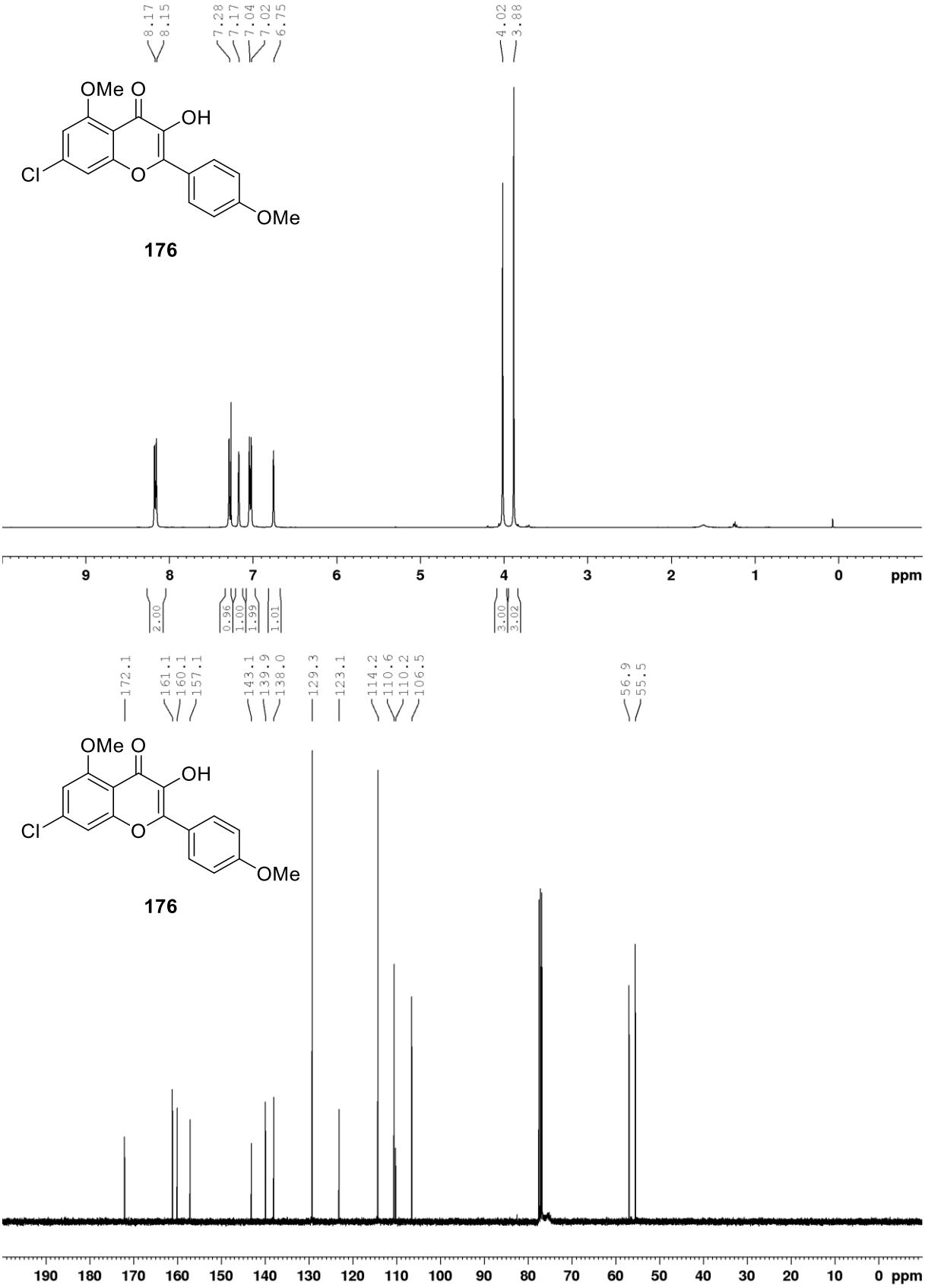
1-(4-Chloro-2-hydroxy-6-methoxyphenyl)ethan-1-one (168)



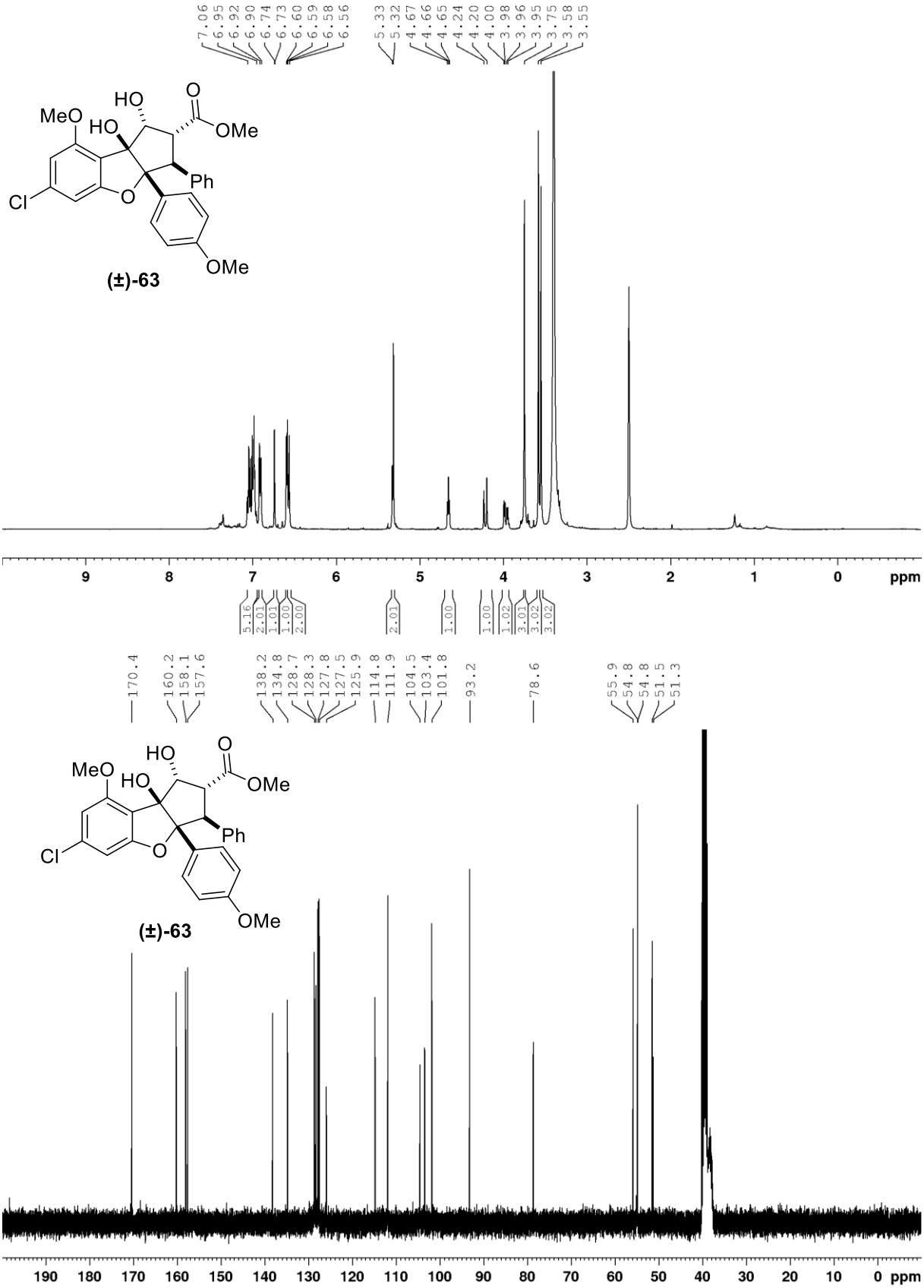
(*E*)-1-(4-Chloro-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (172)



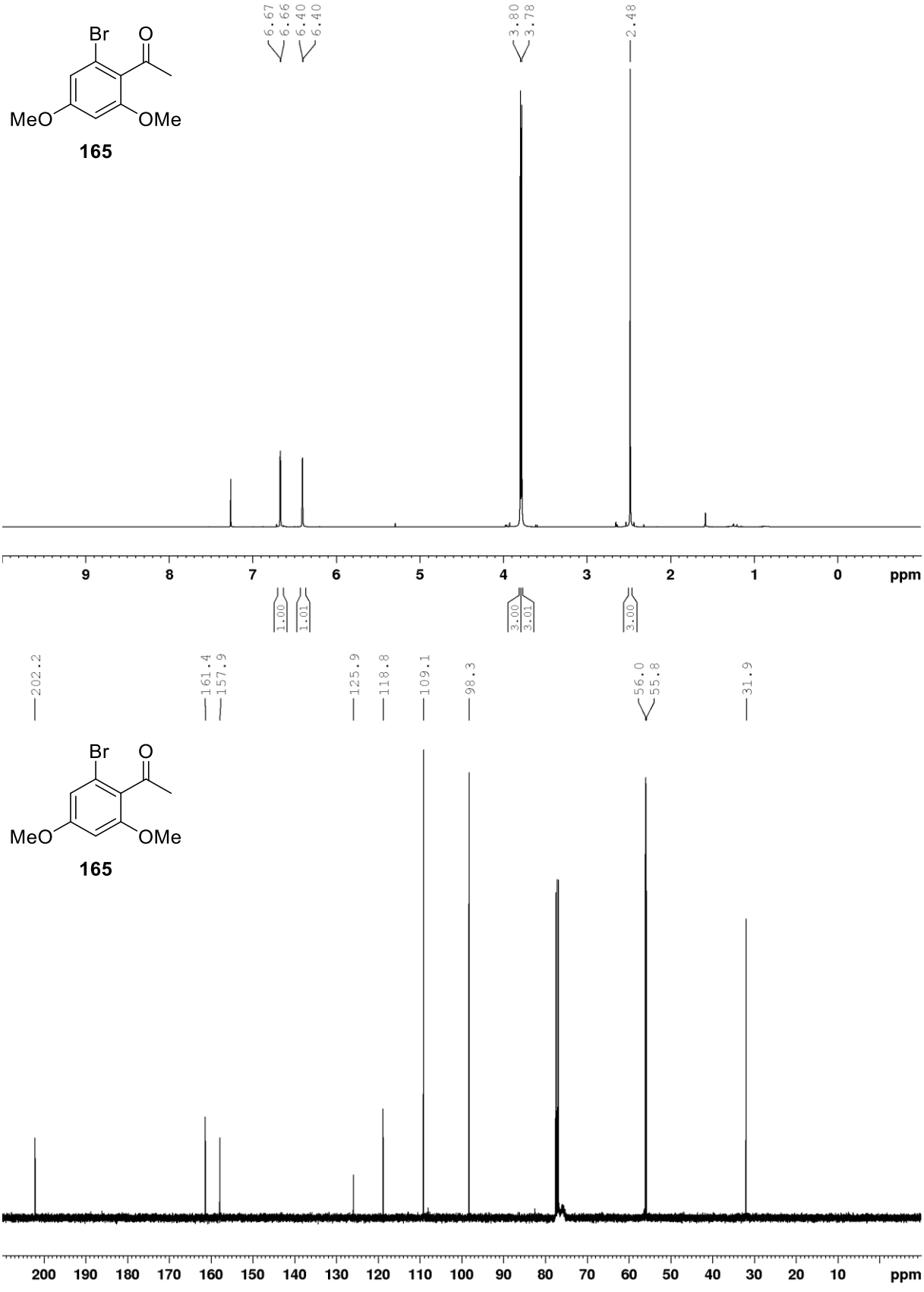
7-Chloro-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (176)



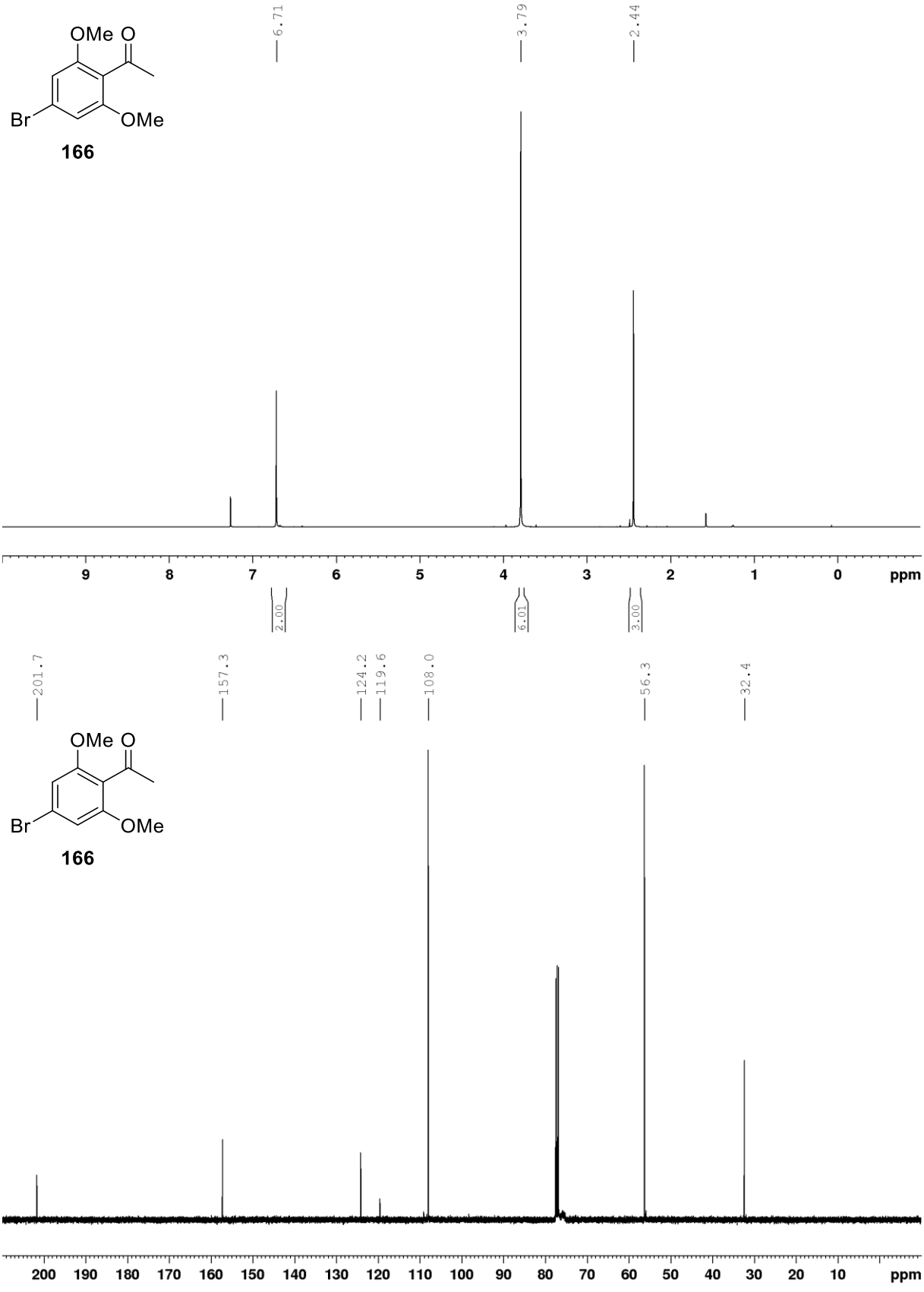
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-63)



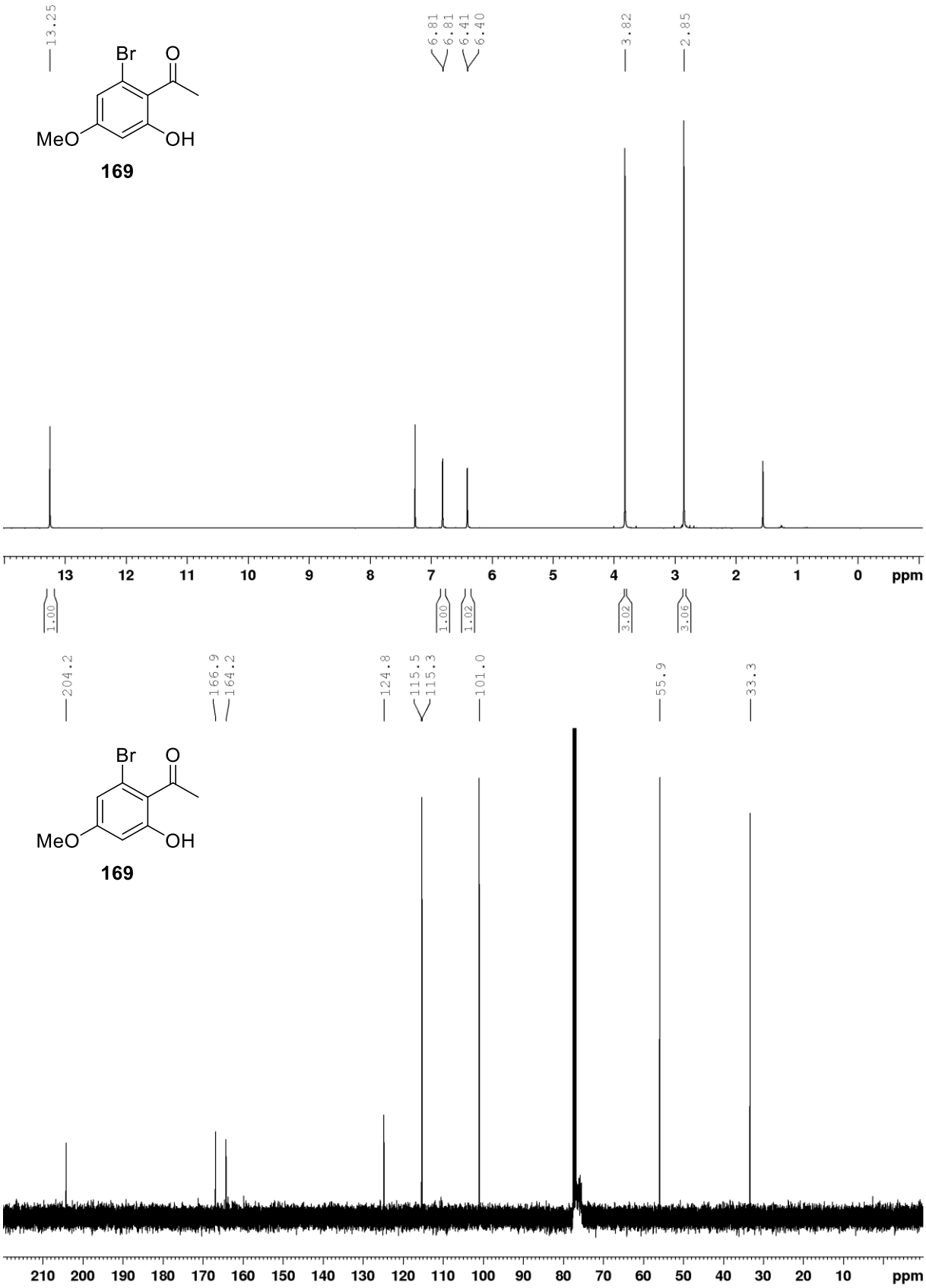
1-(2-Bromo-4,6-dimethoxyphenyl)ethan-1-one (165)



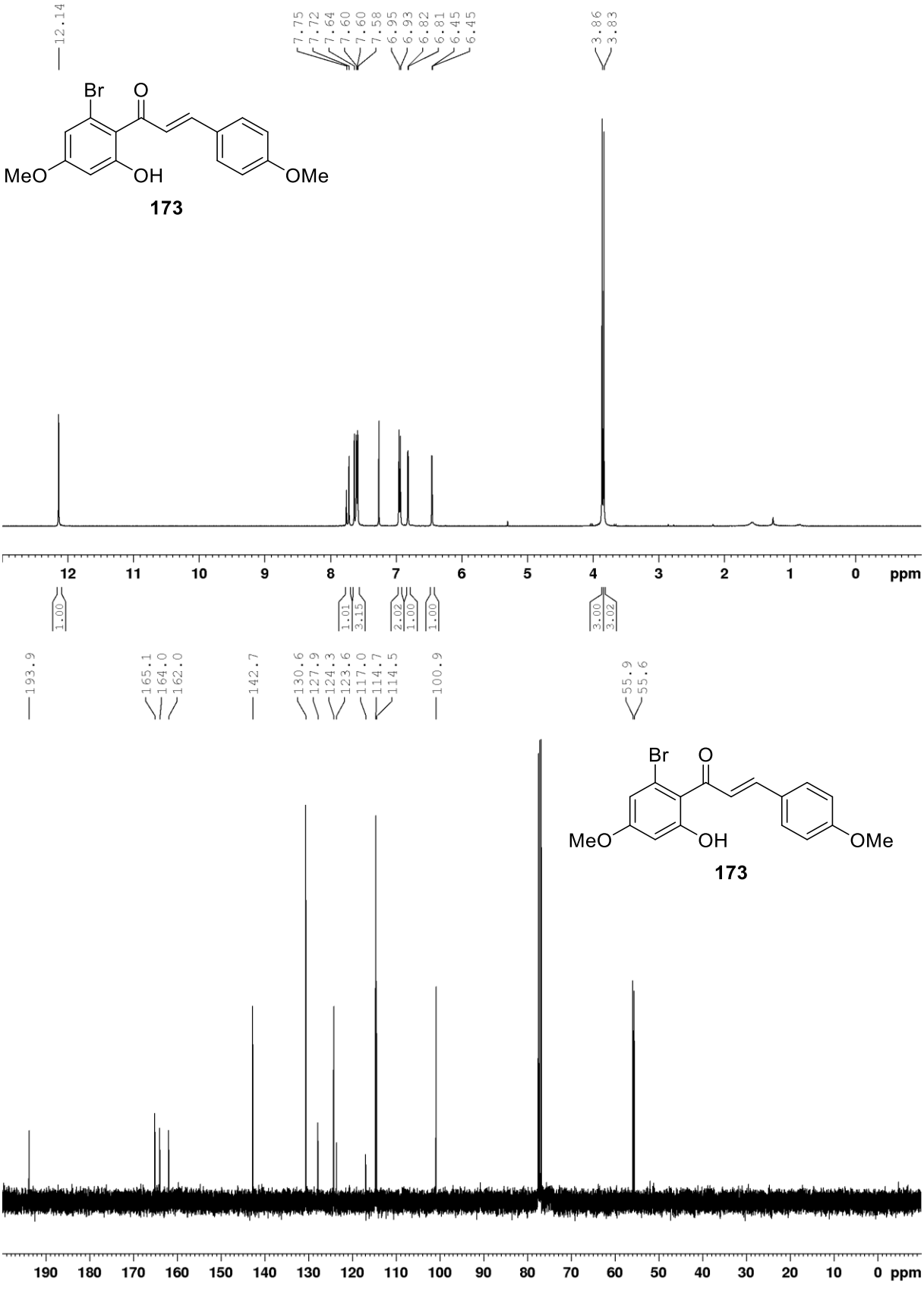
1-(4-Bromo-2,6-dimethoxyphenyl)ethan-1-one (166)



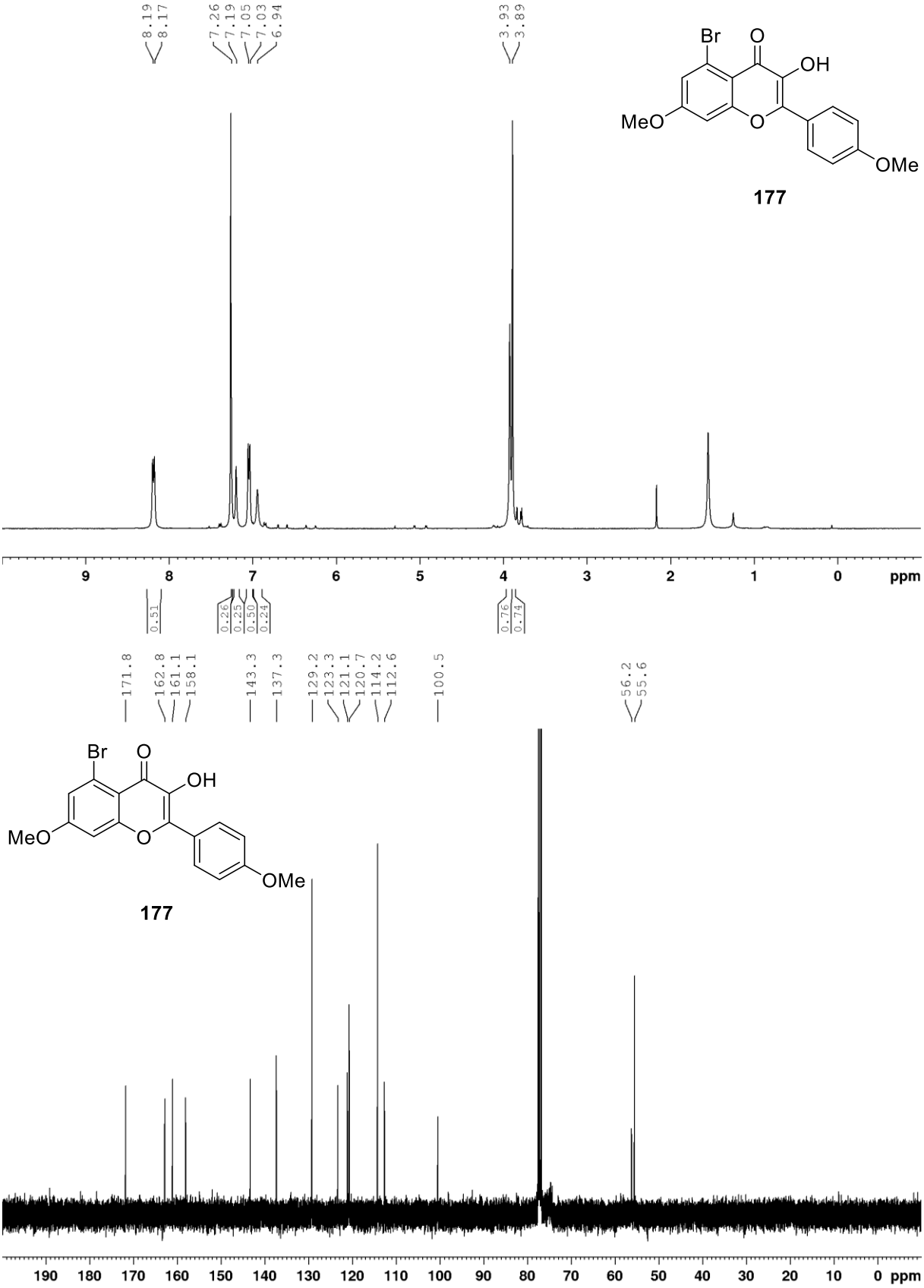
1-(2-Bromo-6-hydroxy-4-methoxyphenyl)ethan-1-one (169)



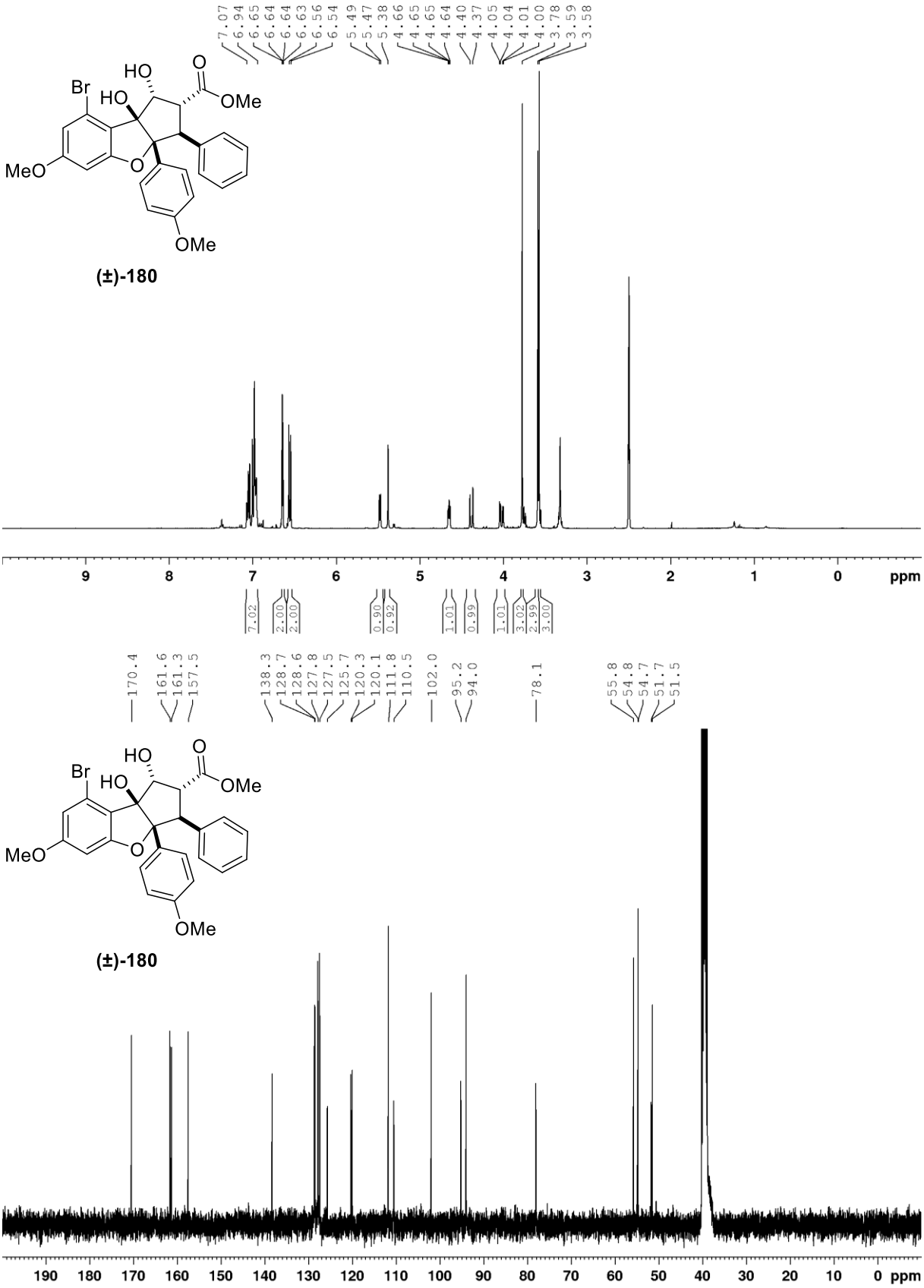
(*E*)-1-(2-Bromo-6-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (173)



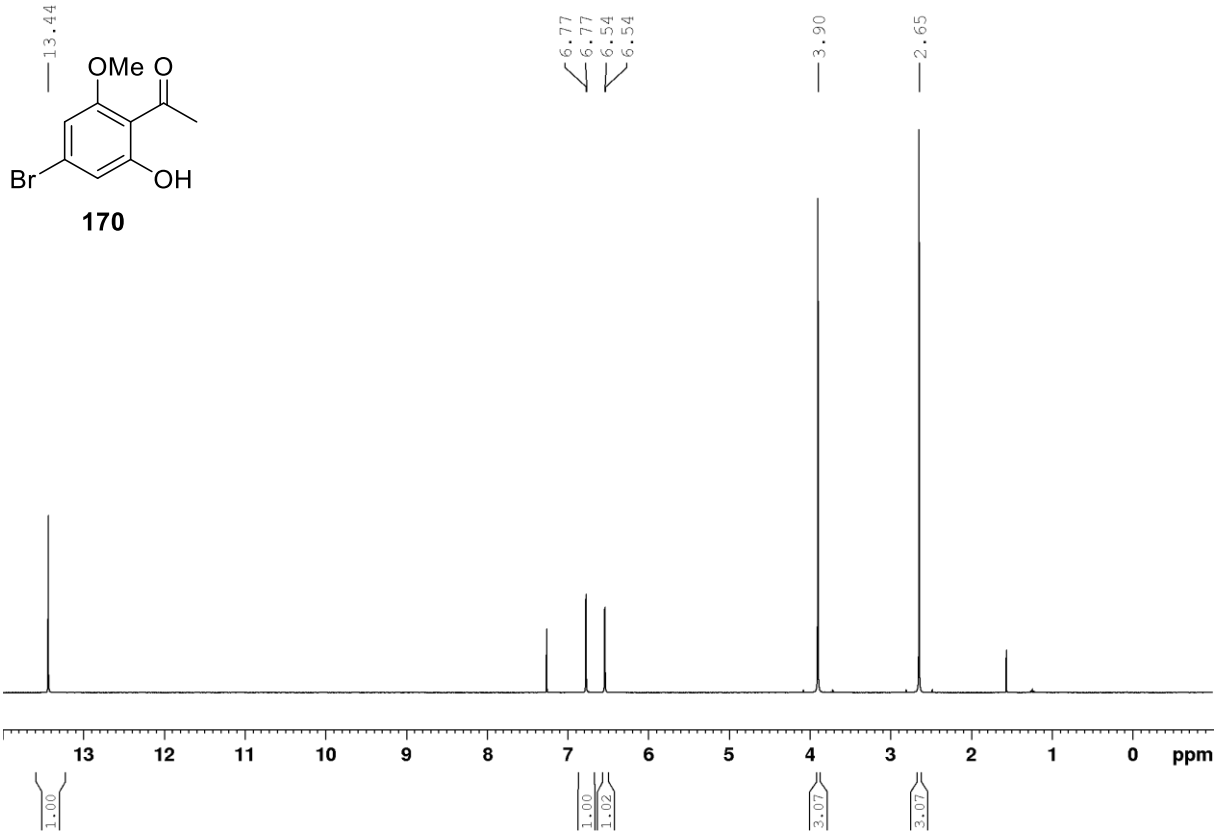
5-Bromo-3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (177)

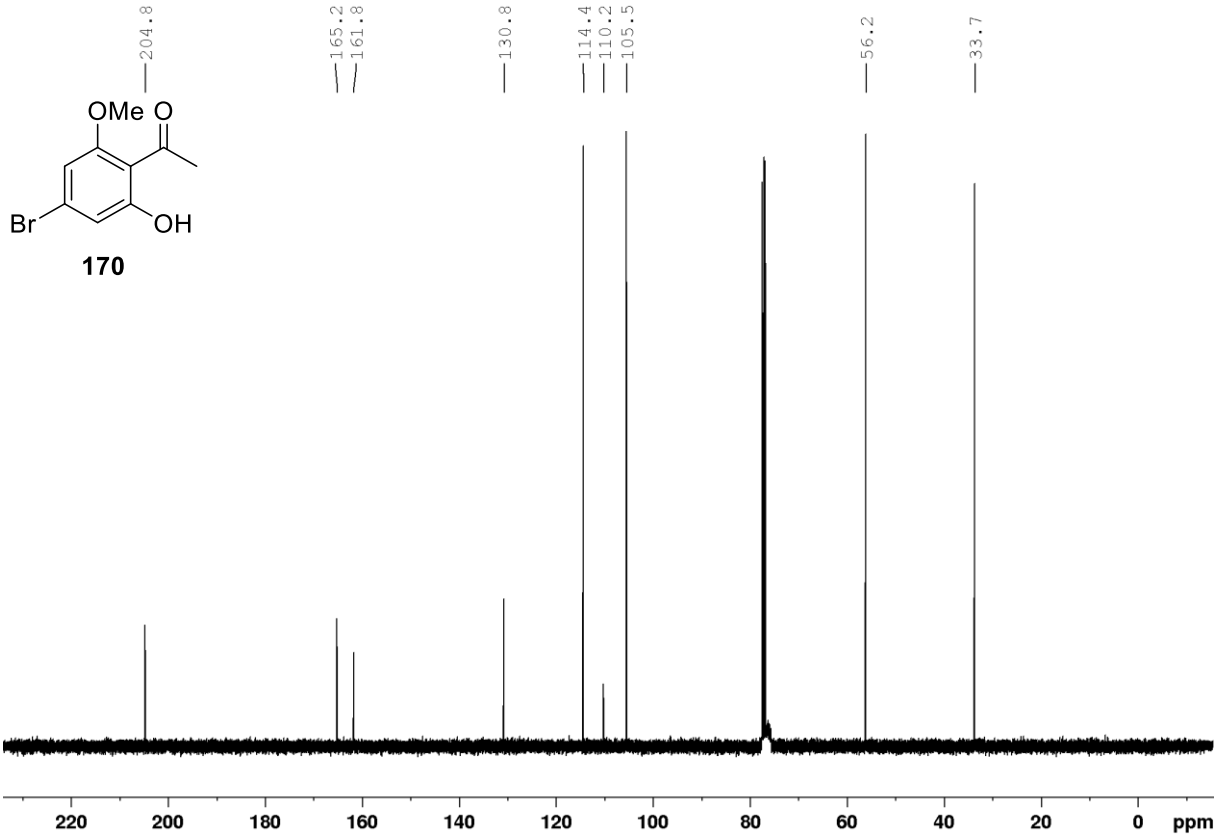


(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-8-bromo-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-180)

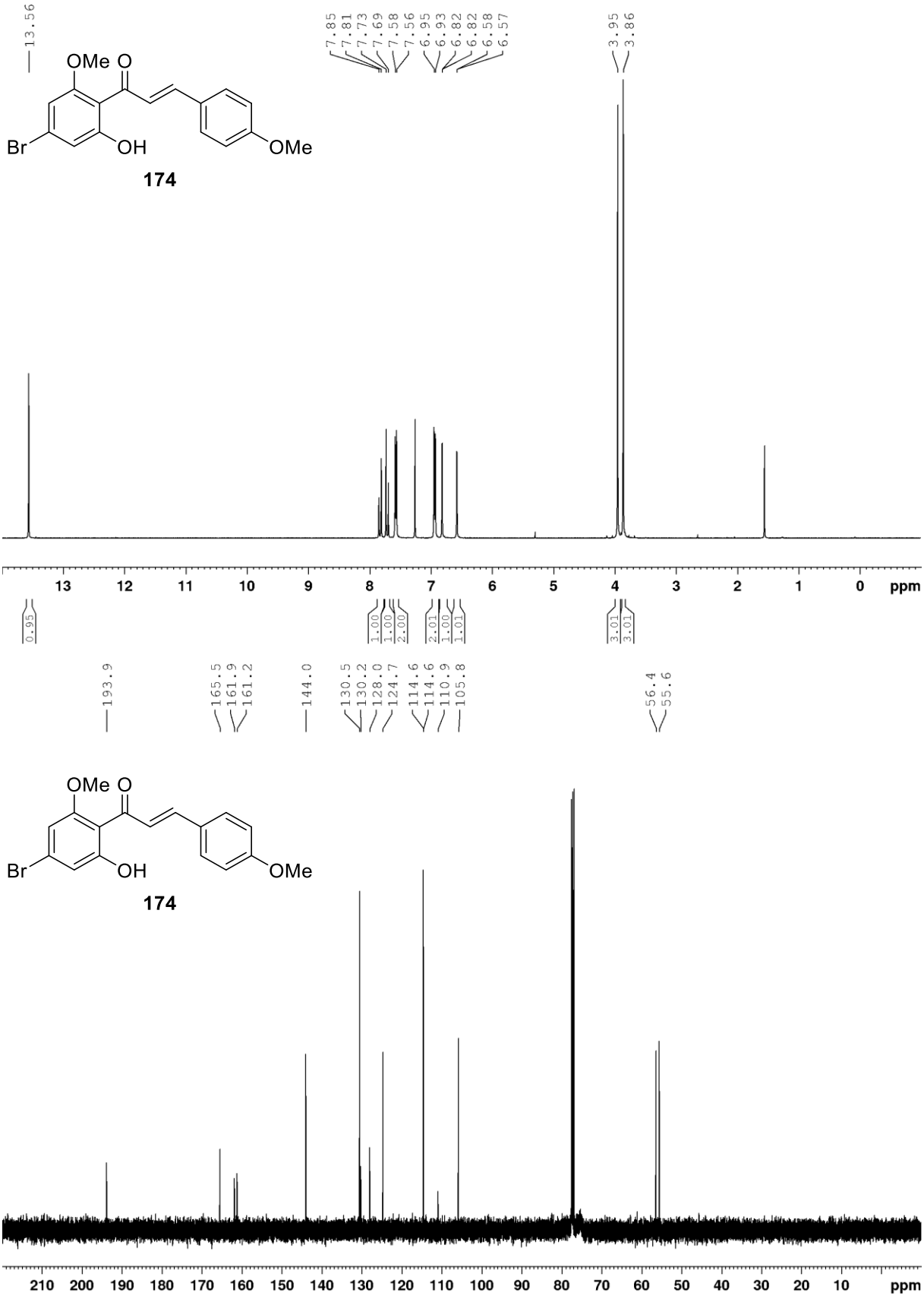


1-(4-Bromo-2-hydroxy-6-methoxyphenyl)ethan-1-one (170)

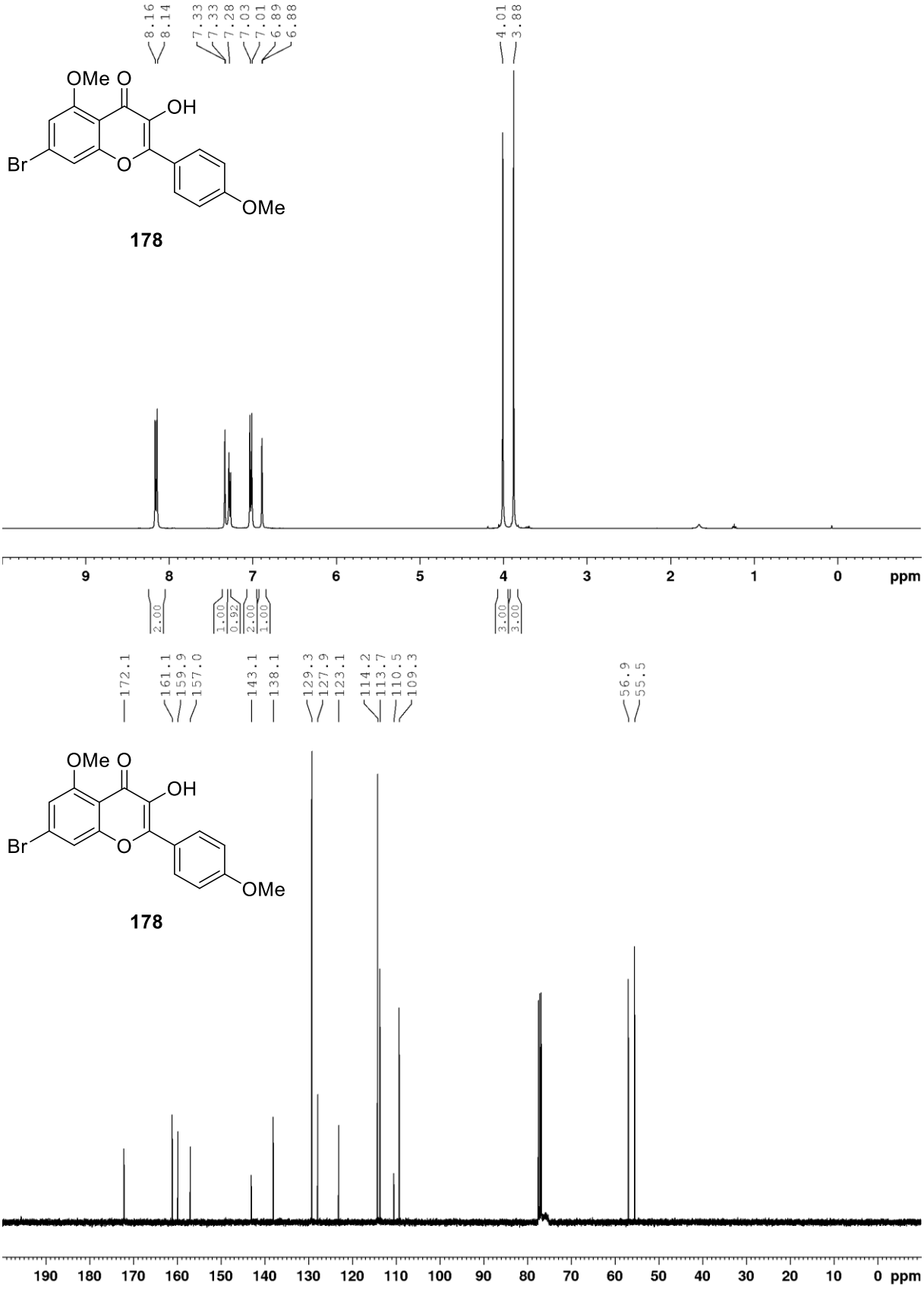




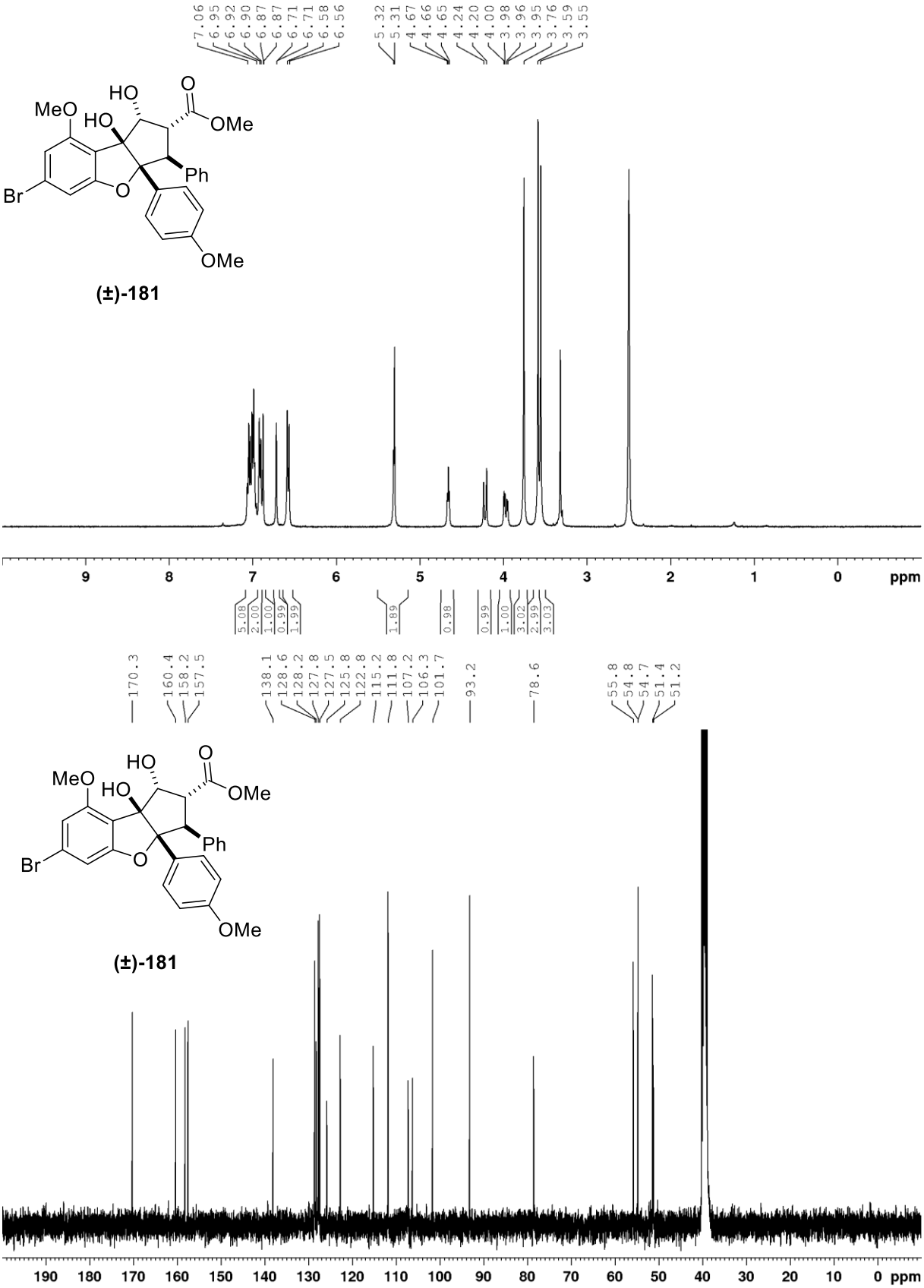
(*E*)-1-(4-Bromo-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (174)



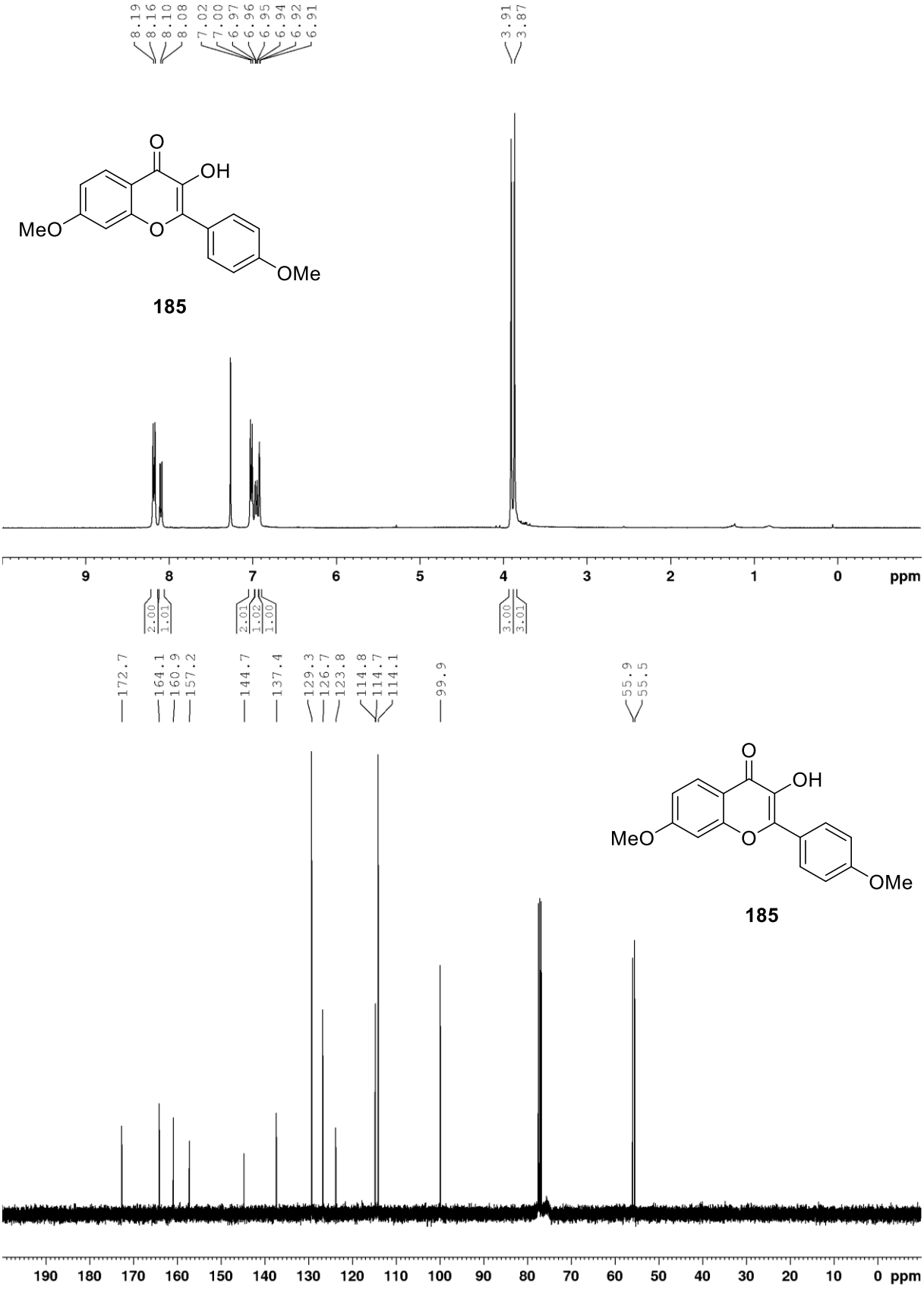
7-Bromo-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (178)



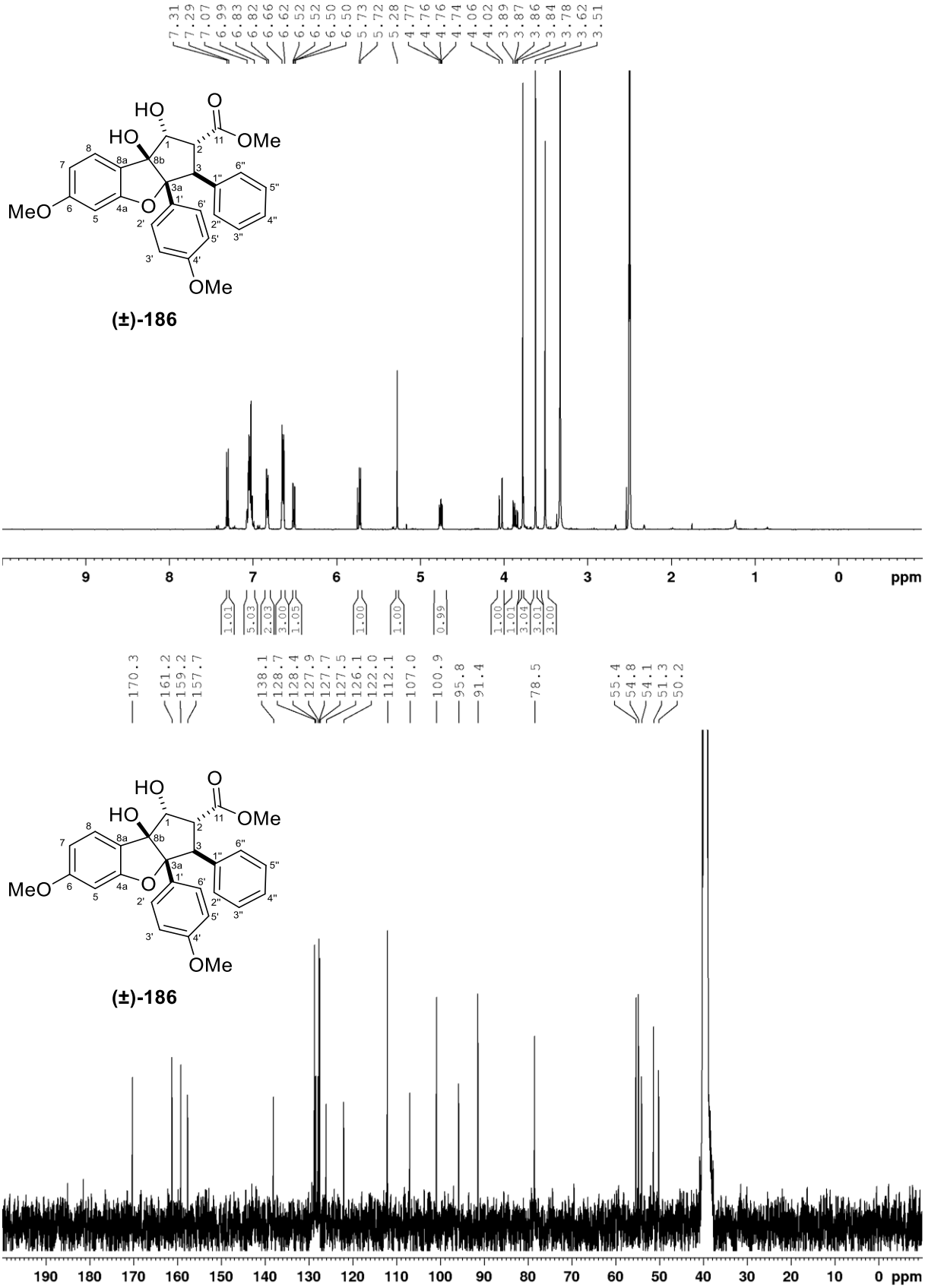
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-bromo-1,8b-dihydroxy-8-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-181)



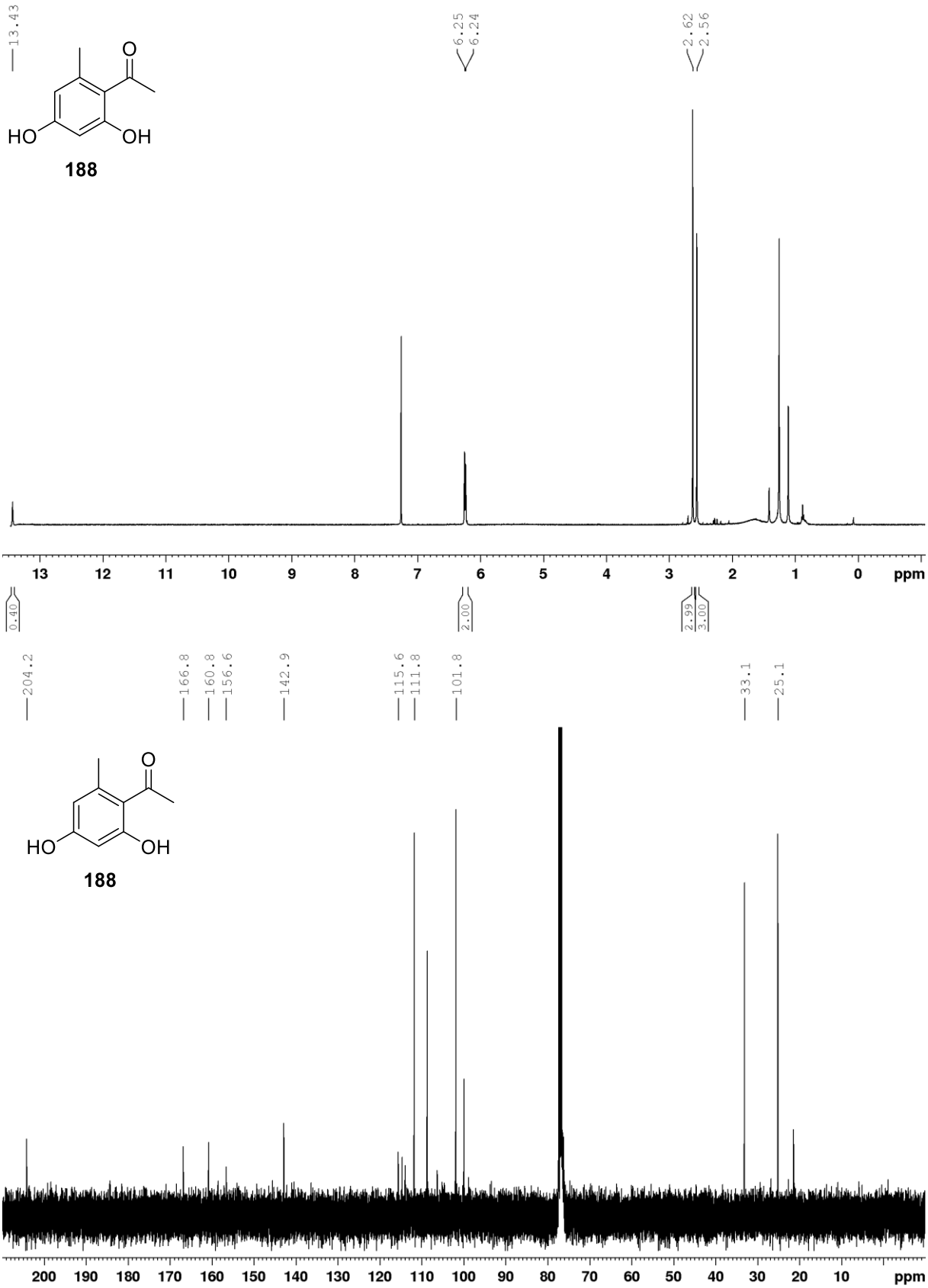
3-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (185)



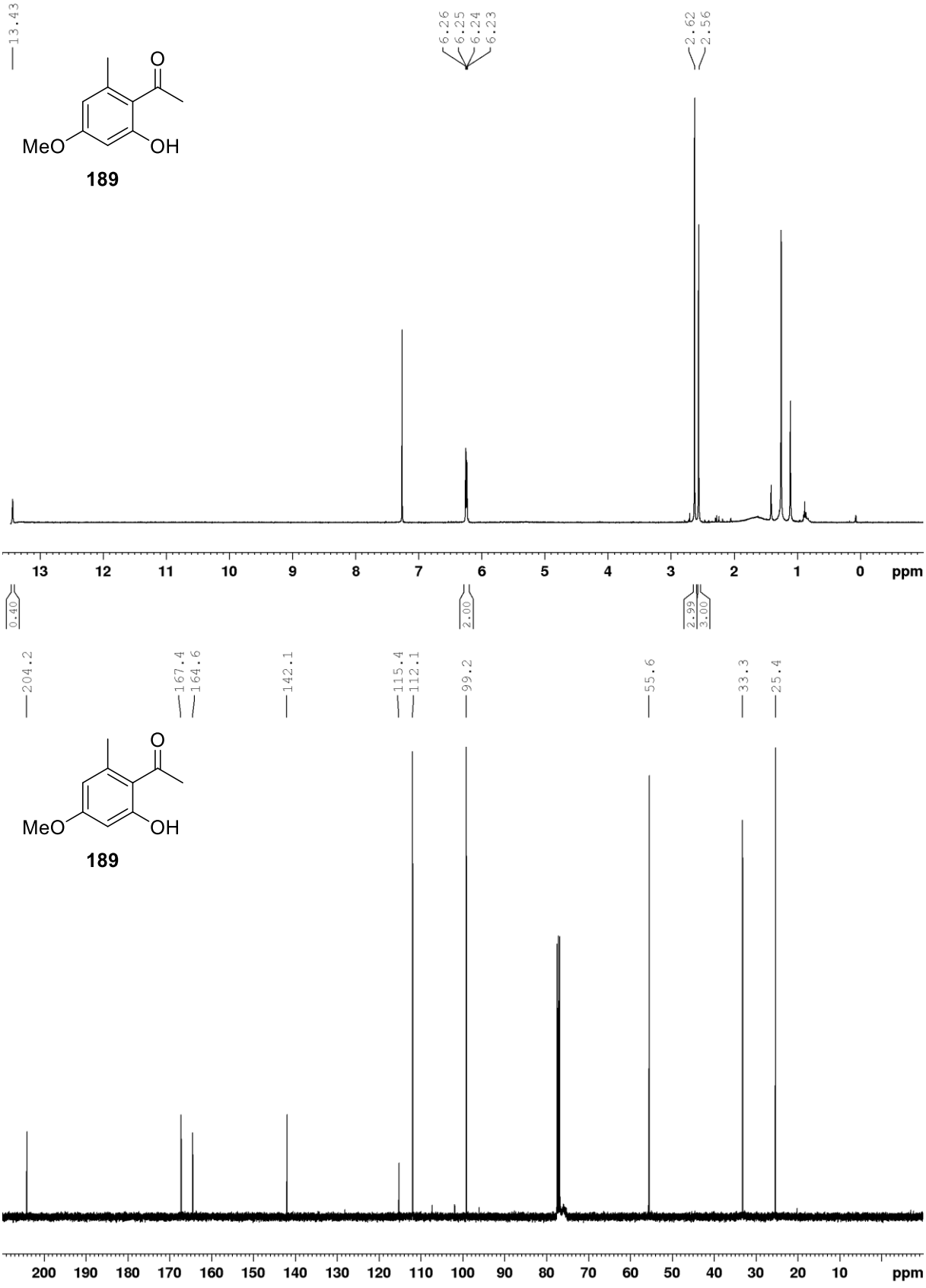
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-186)



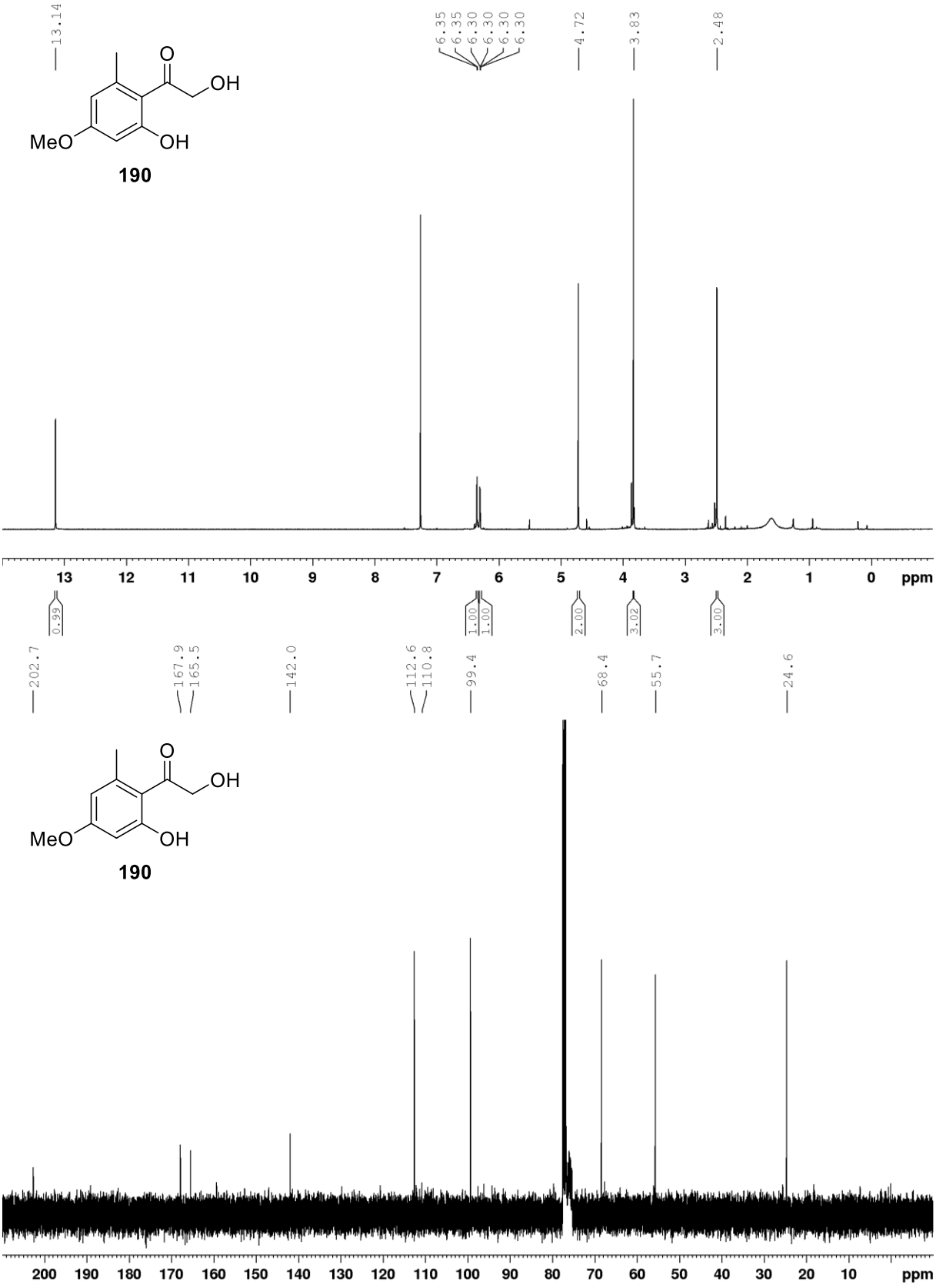
1-(2,4-Dihydroxy-6-methylphenyl)ethan-1-one (188)



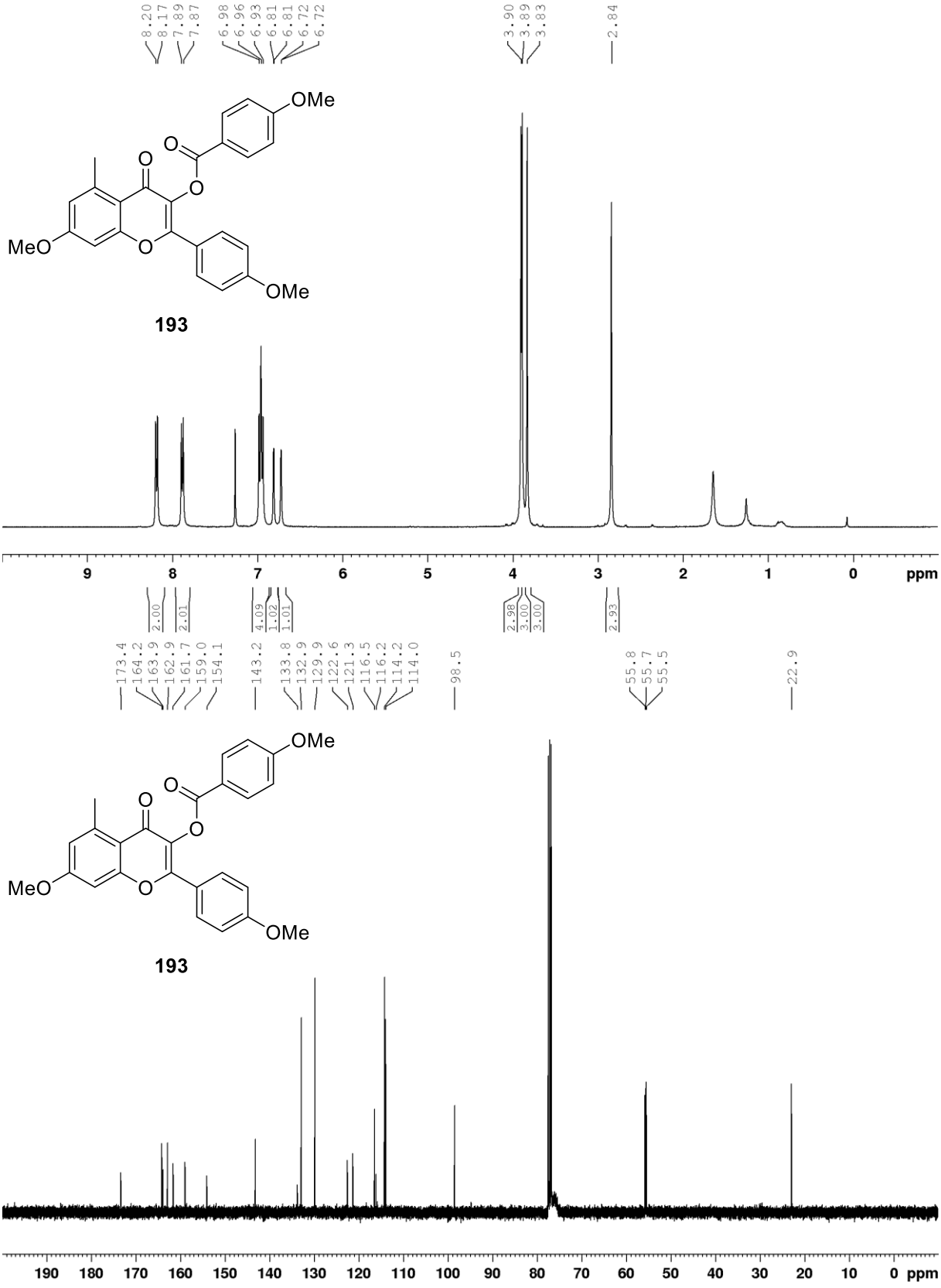
1-(2-Hydroxy-4-methoxy-6-methylphenyl)ethan-1-one (189)



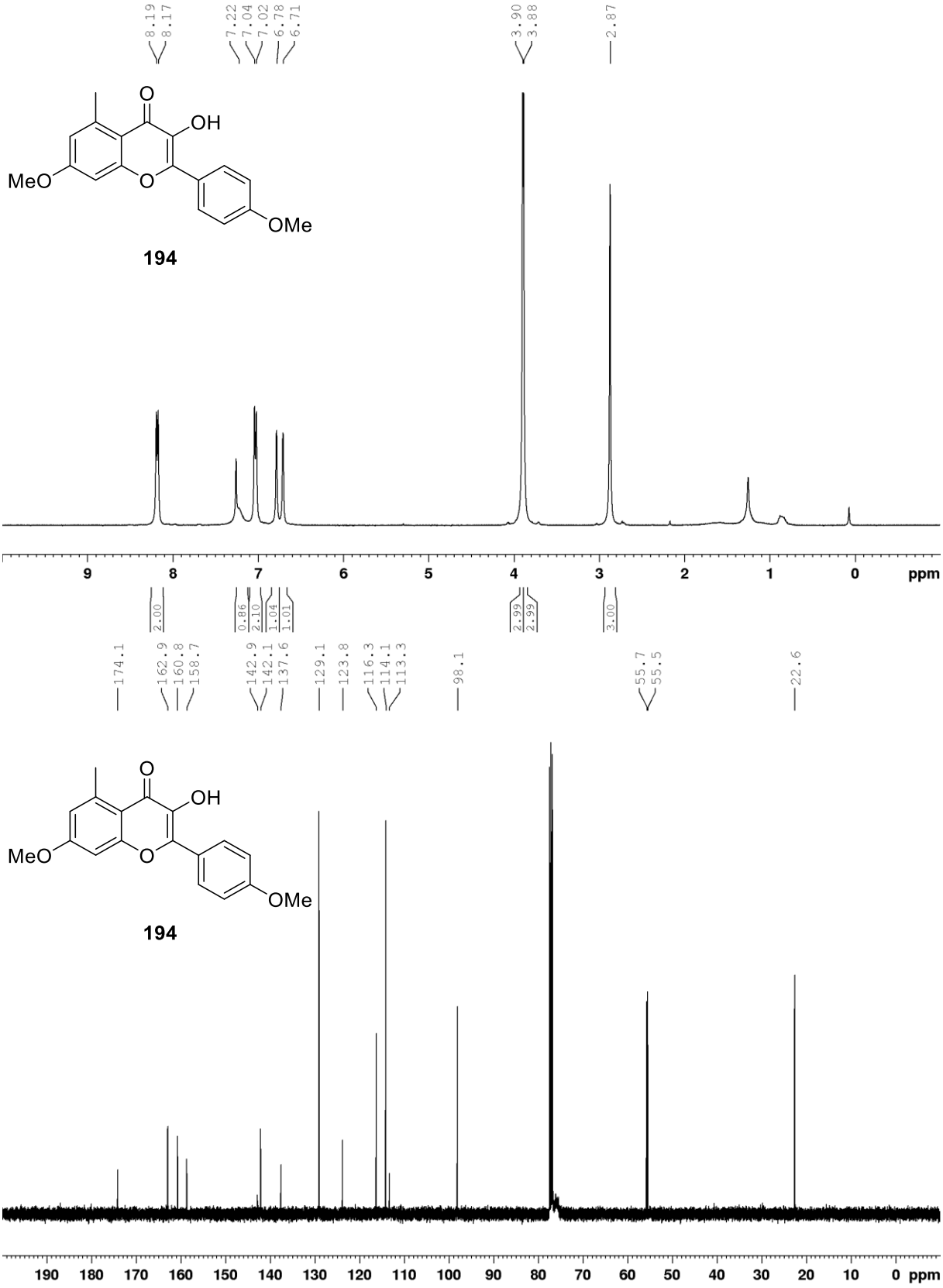
2-Hydroxy-1-(2-hydroxy-4-methoxy-6-methylphenyl)ethan-1-one (190)



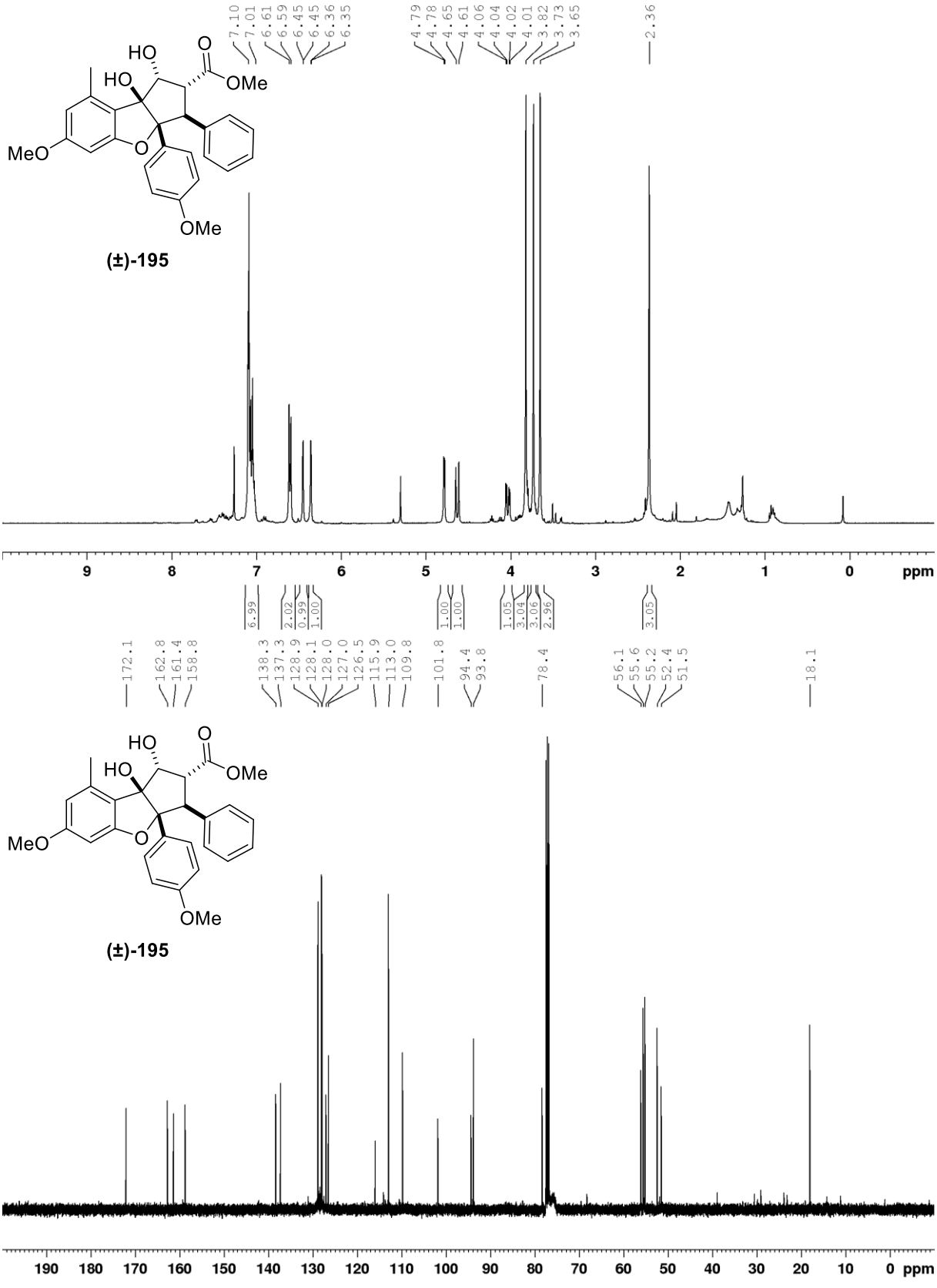
7-Methoxy-2-(4-methoxyphenyl)-5-methyl-4-oxo-4*H*-chromen-3-yl 4-methoxybenzoate (193)



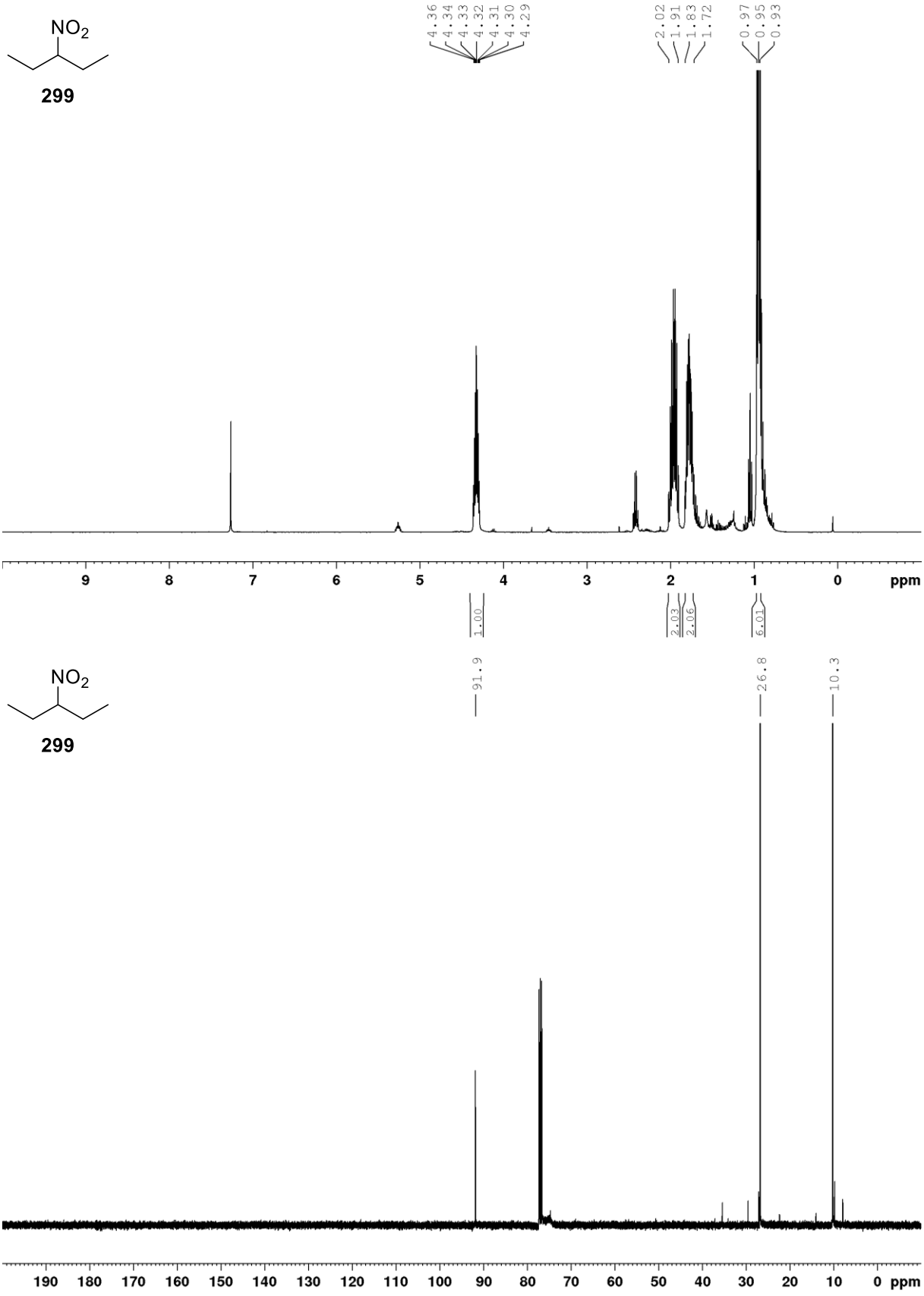
3-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-5-methyl-4*H*-chromen-4-one (194)



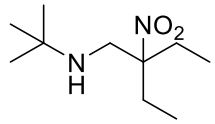
(±)-Methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-8-methyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate ((±)-195)



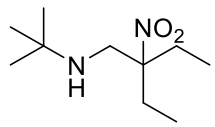
3-Nitropentane (299)



_N_-(_tert_-Butyl)-2-ethyl-2-nitrobutan-1-amine (300)

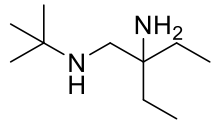


300



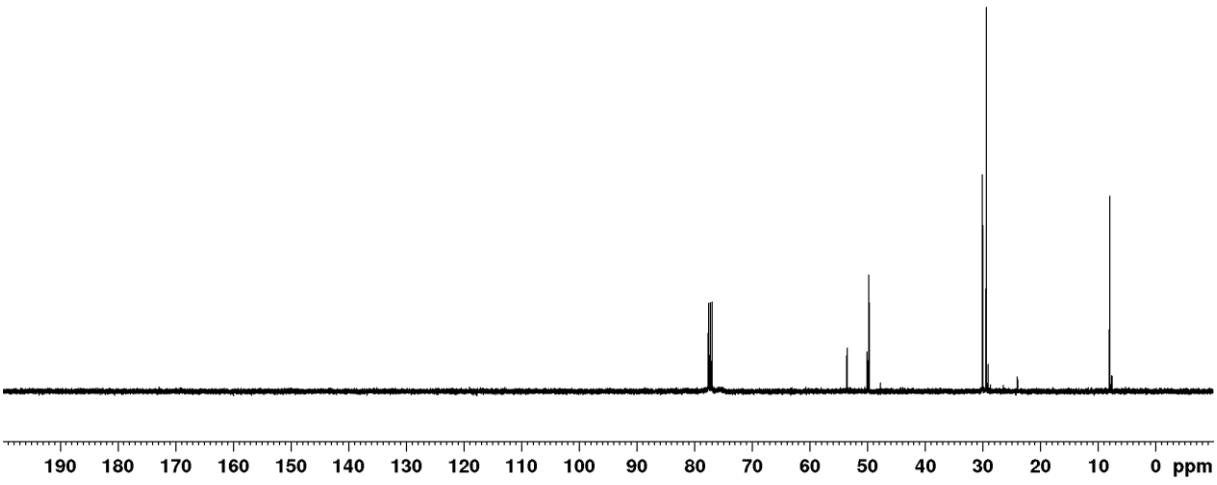
300

N^1-(*tert*-Butyl)-2-ethylbutane-1,2-diamine (301)

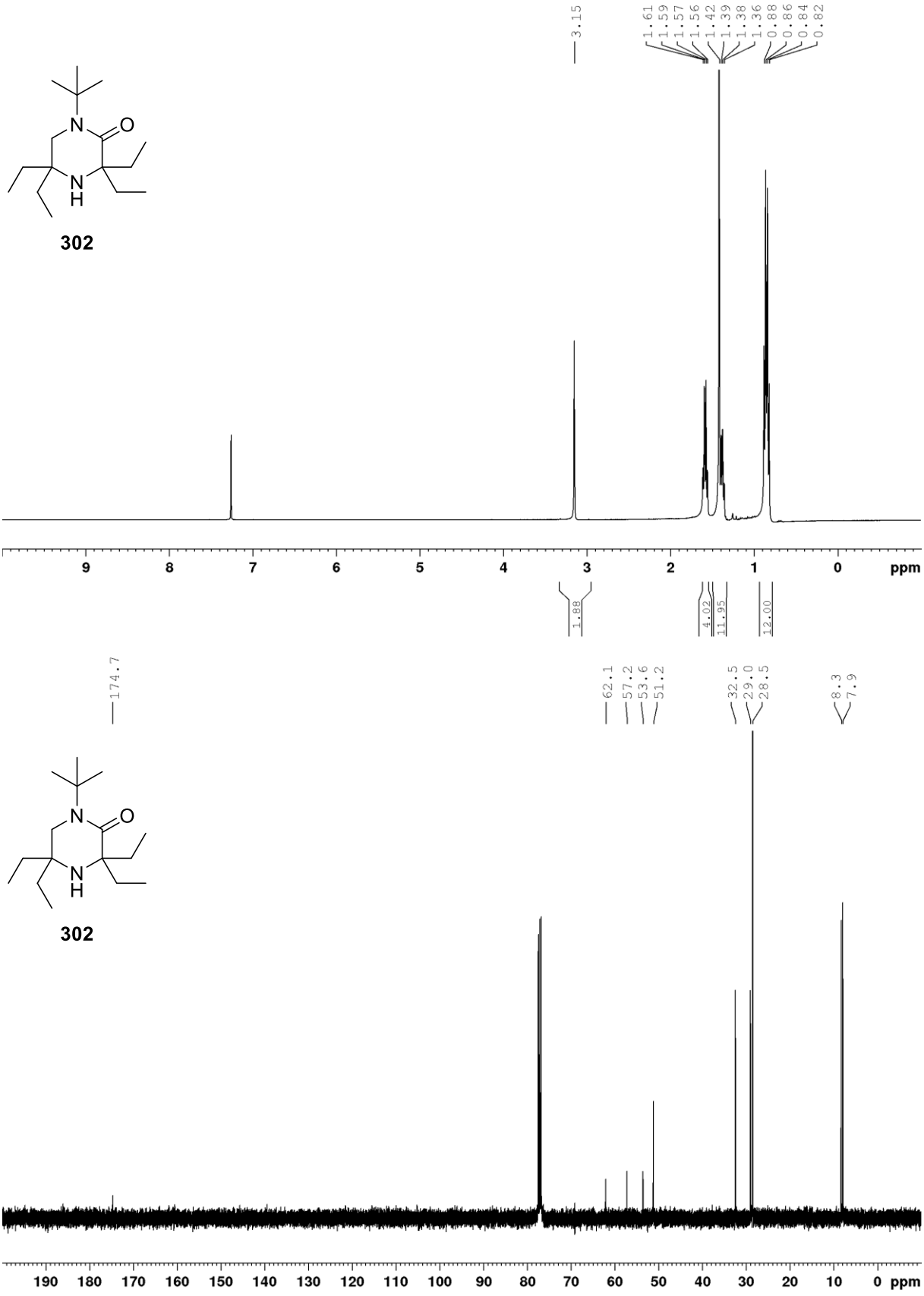


301

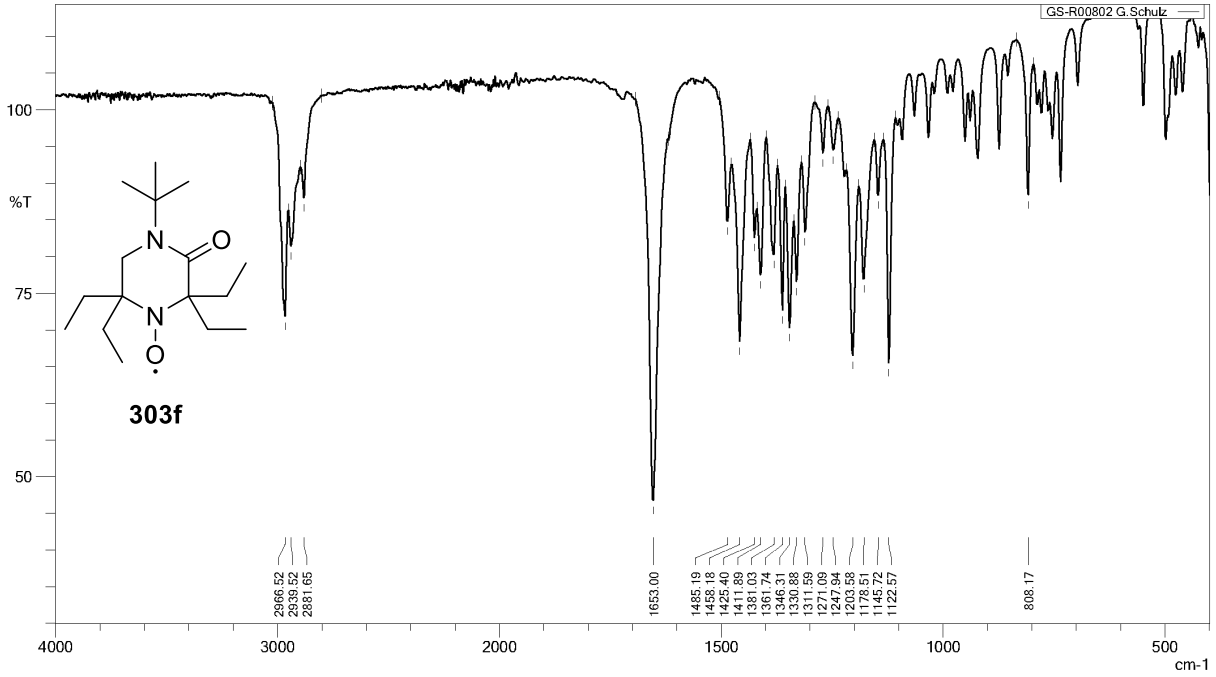
301



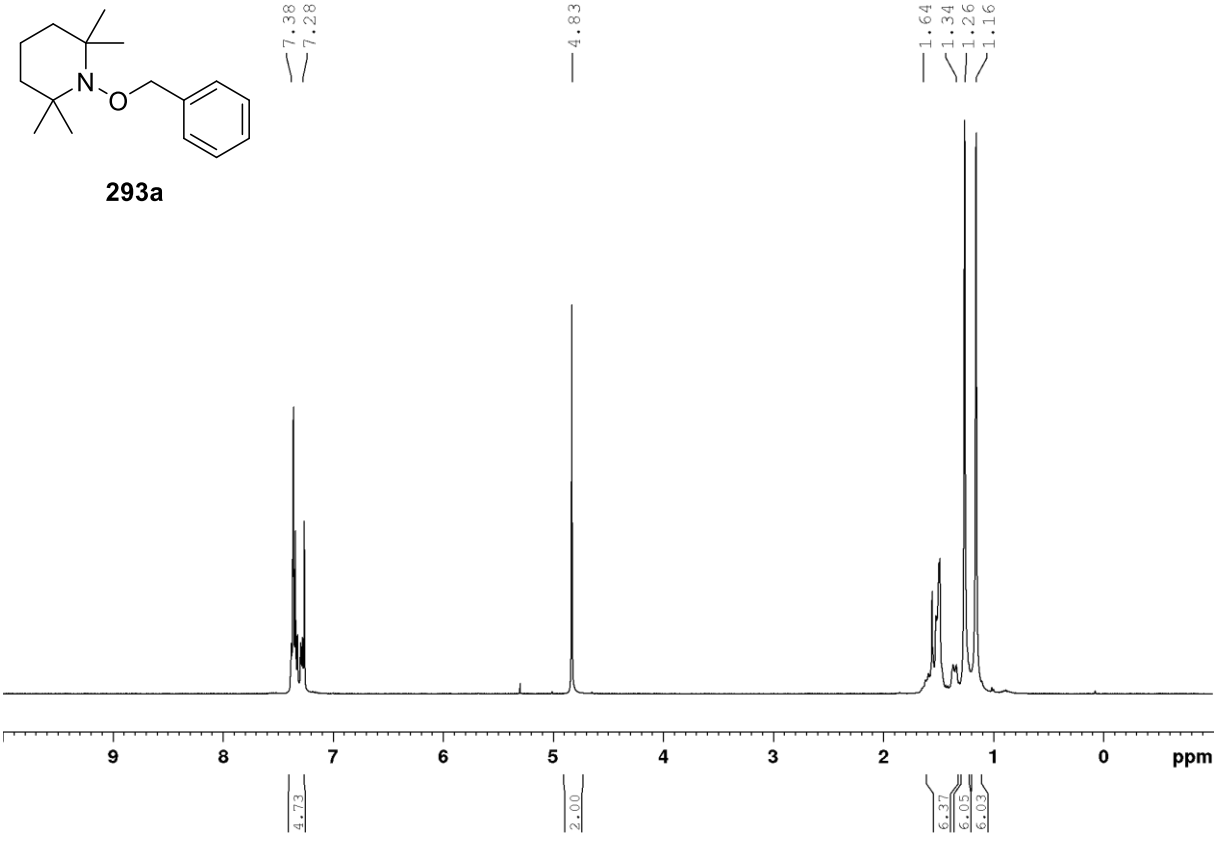
1-(*tert*-Butyl)-3,3,5,5-tetraethylpiperazin-2-one (302)

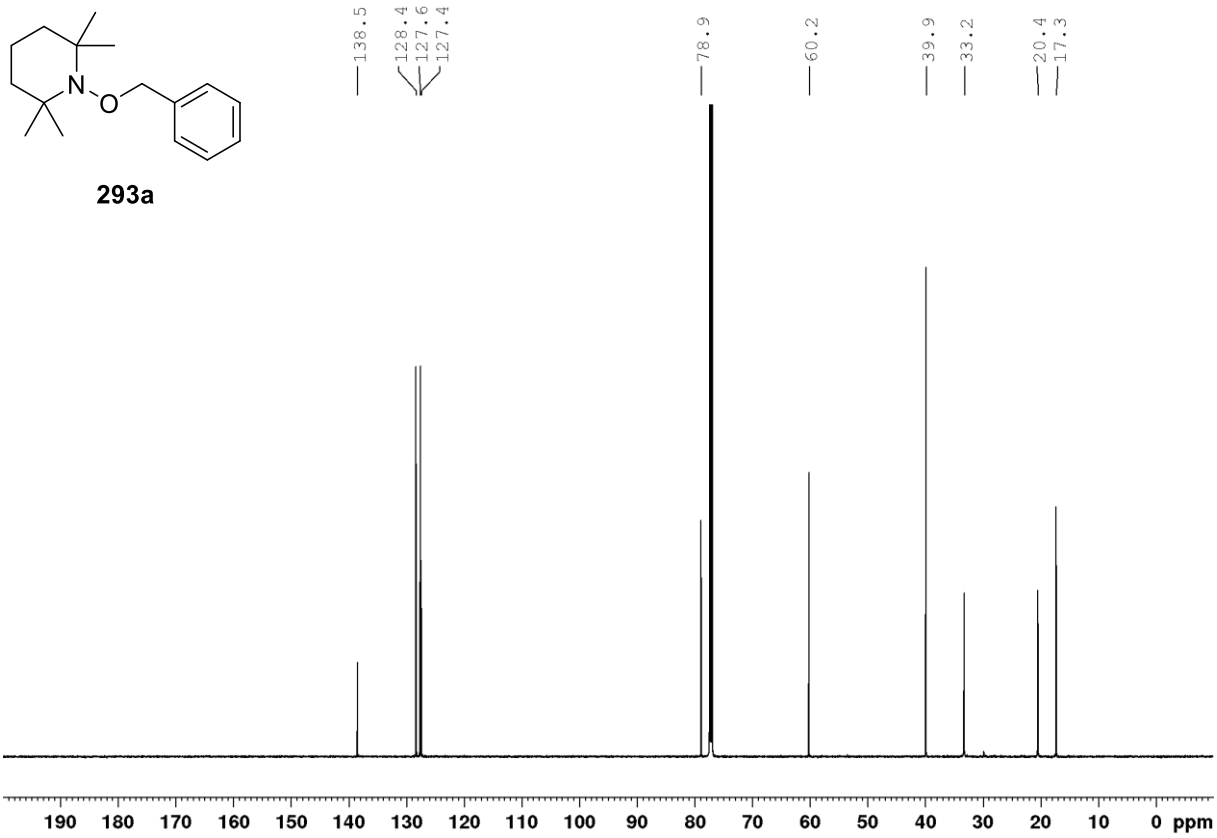


1-*tert*-Butyl-3,3′-diethyl-5,5′-dimethyl-2-piperazinon-4-oxyl (303f)



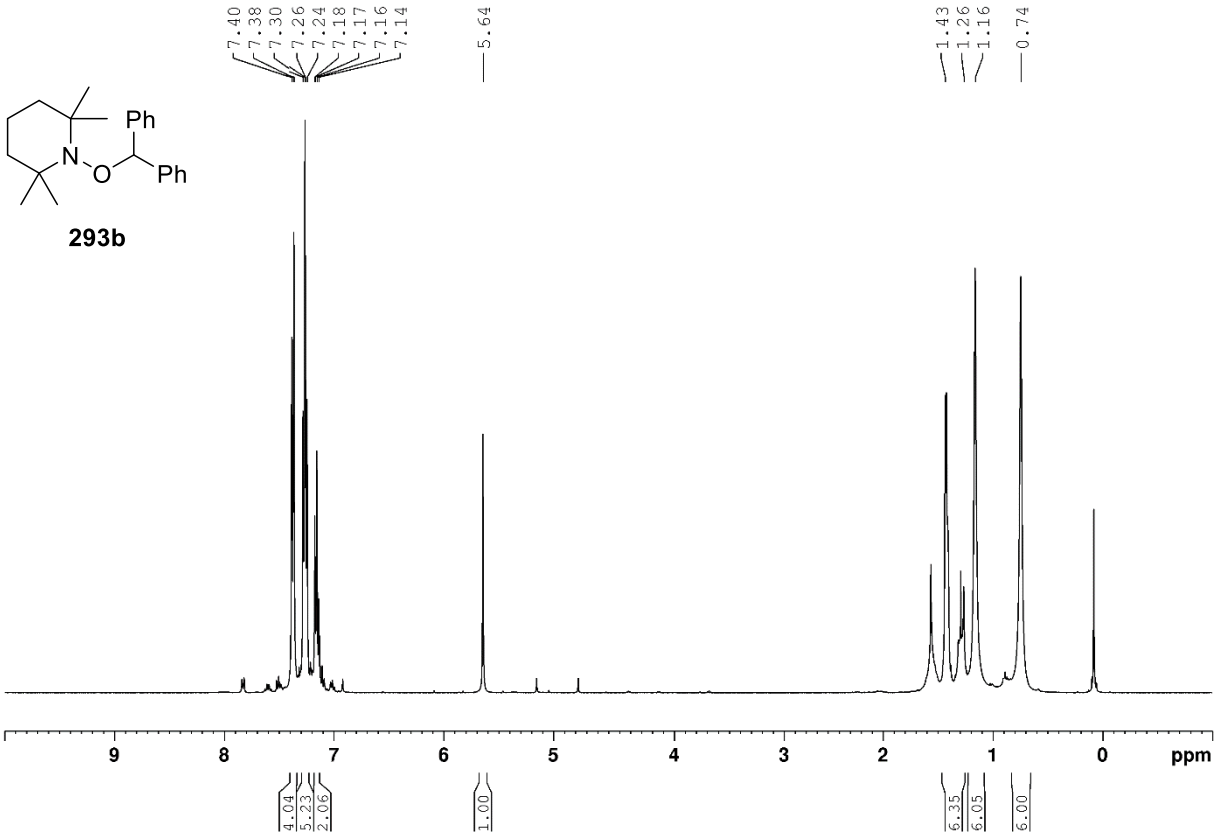
1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (293a)



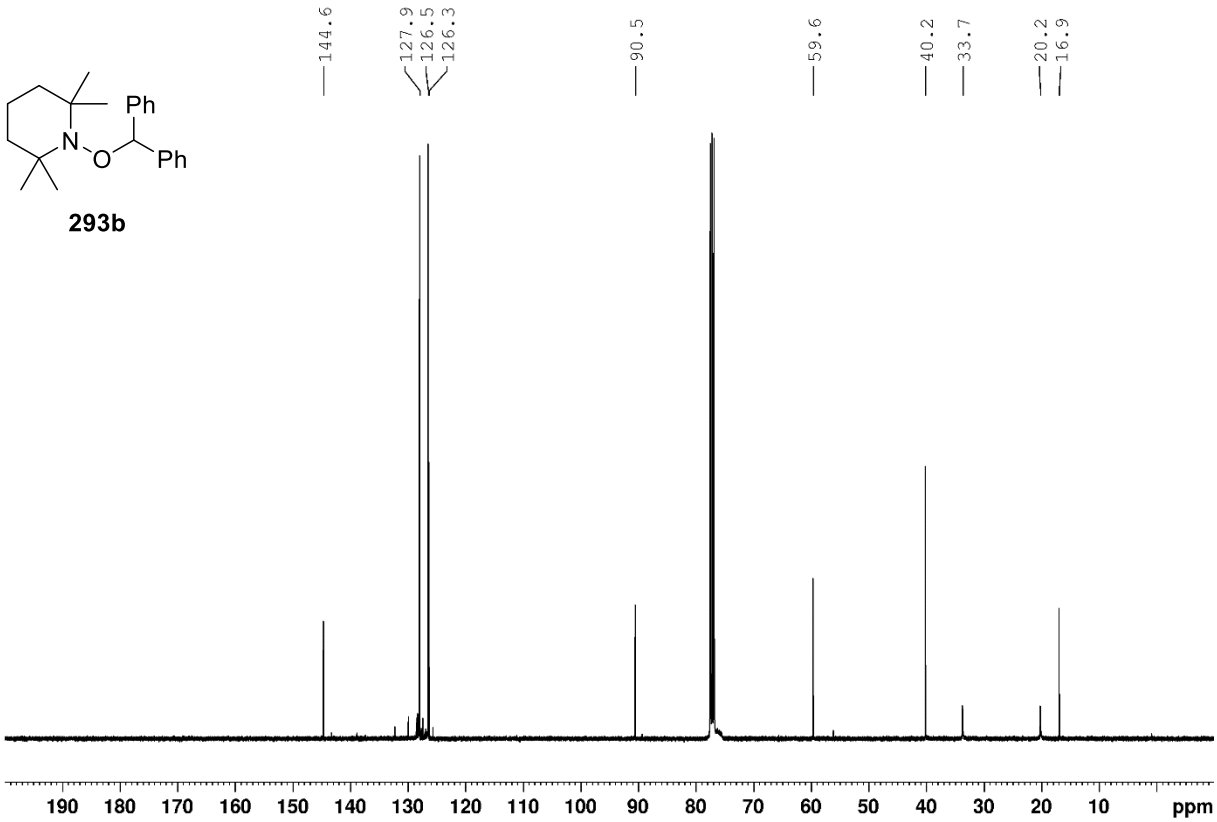


293a

1-(Benzhydryloxy)-2,2,6,6-tetramethylpiperidine (293b)

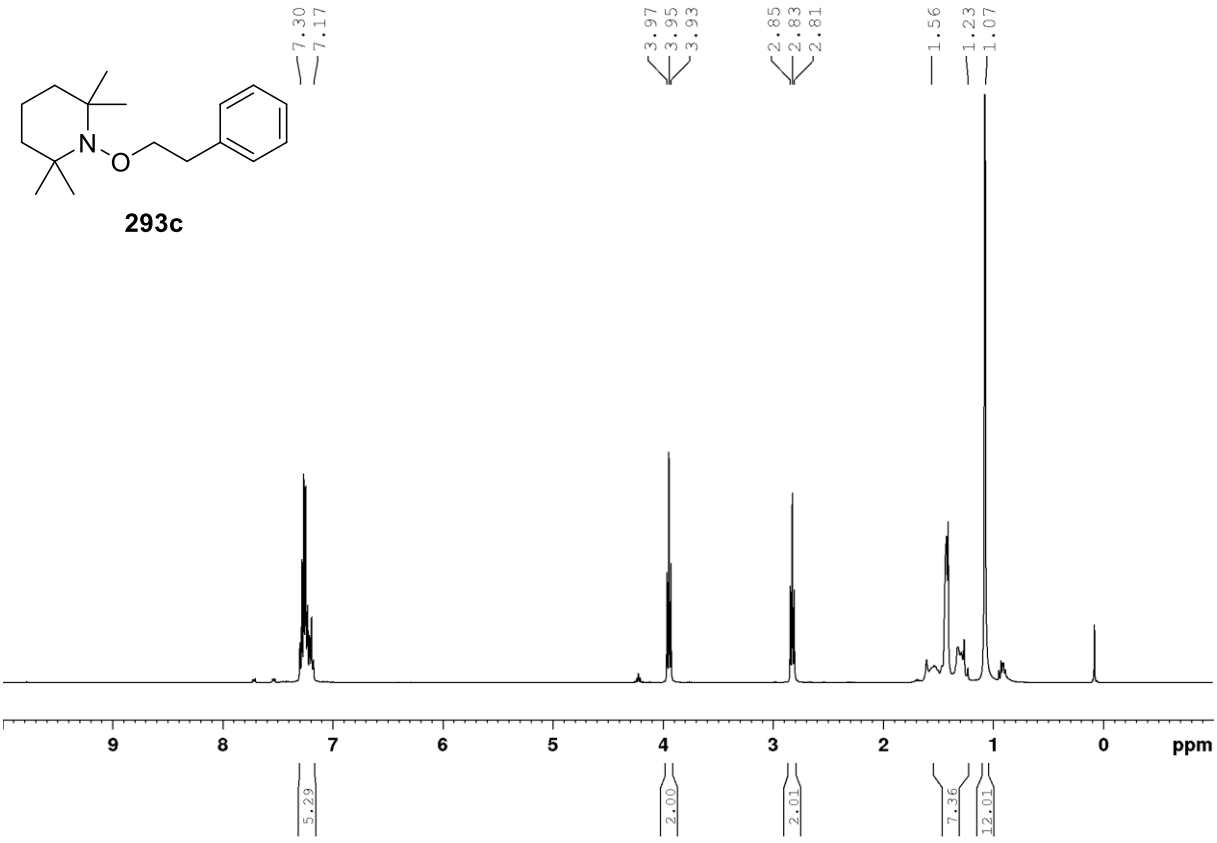


293b

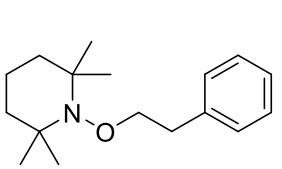


293b

2,2,6,6-Tetramethyl-1-phenethoxypiperidine (293c)

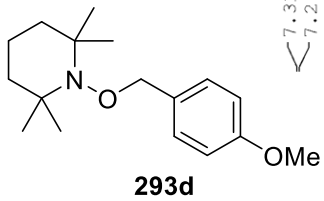


293c

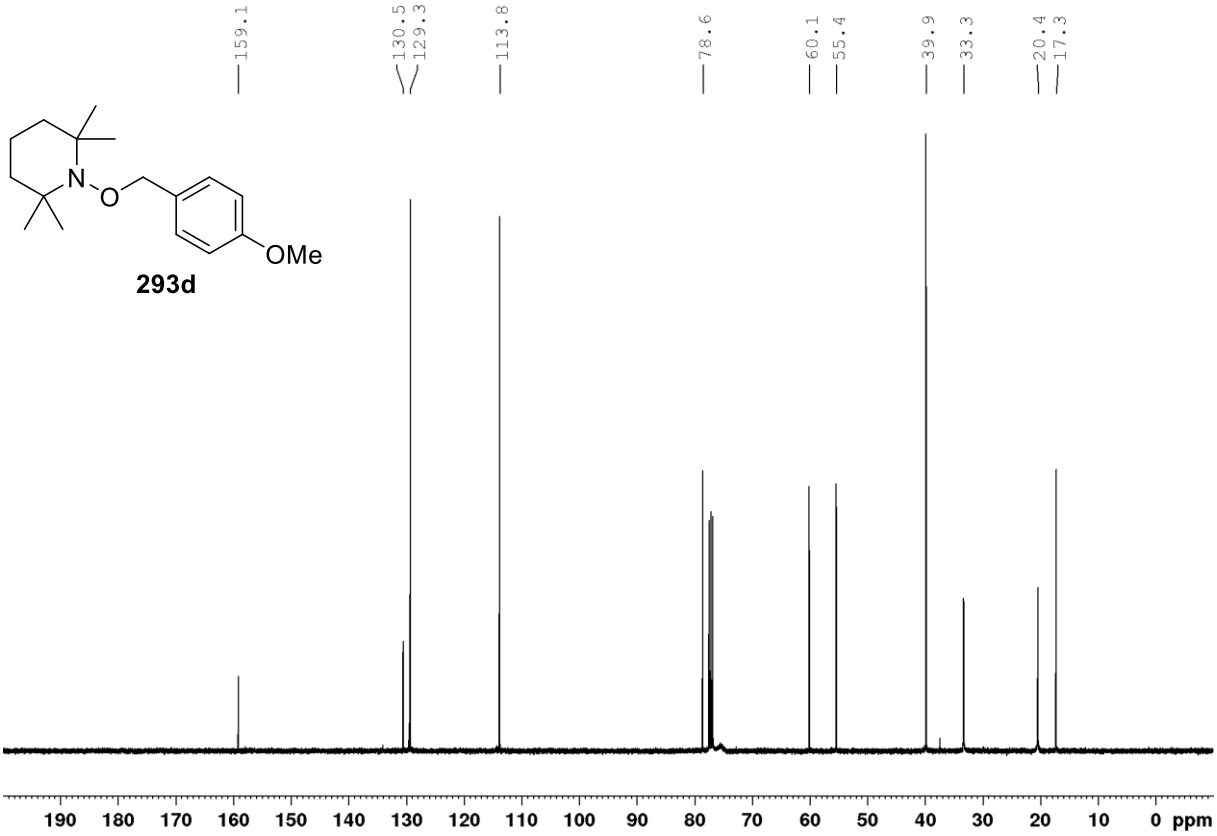


293c

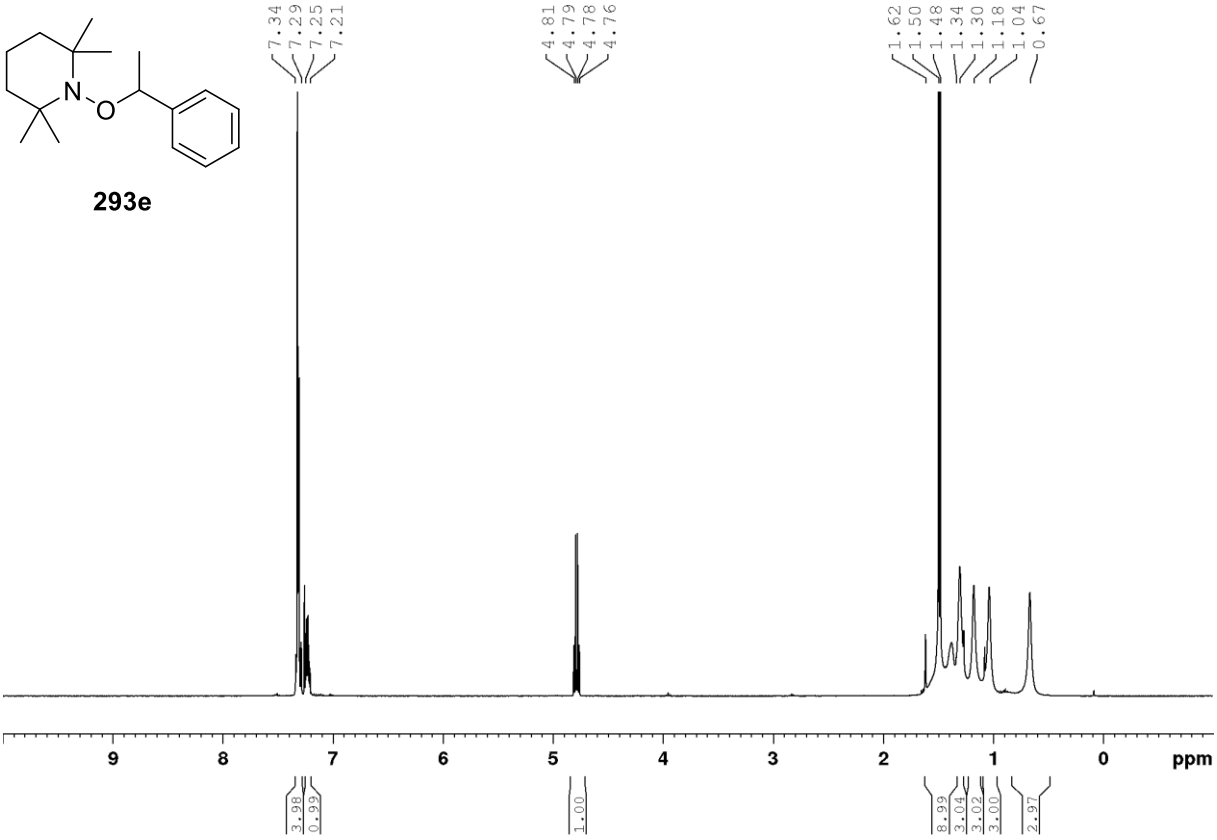
1-((4-Methoxybenzyl)oxy)-2,2,6,6-tetramethylpiperidine (293d)

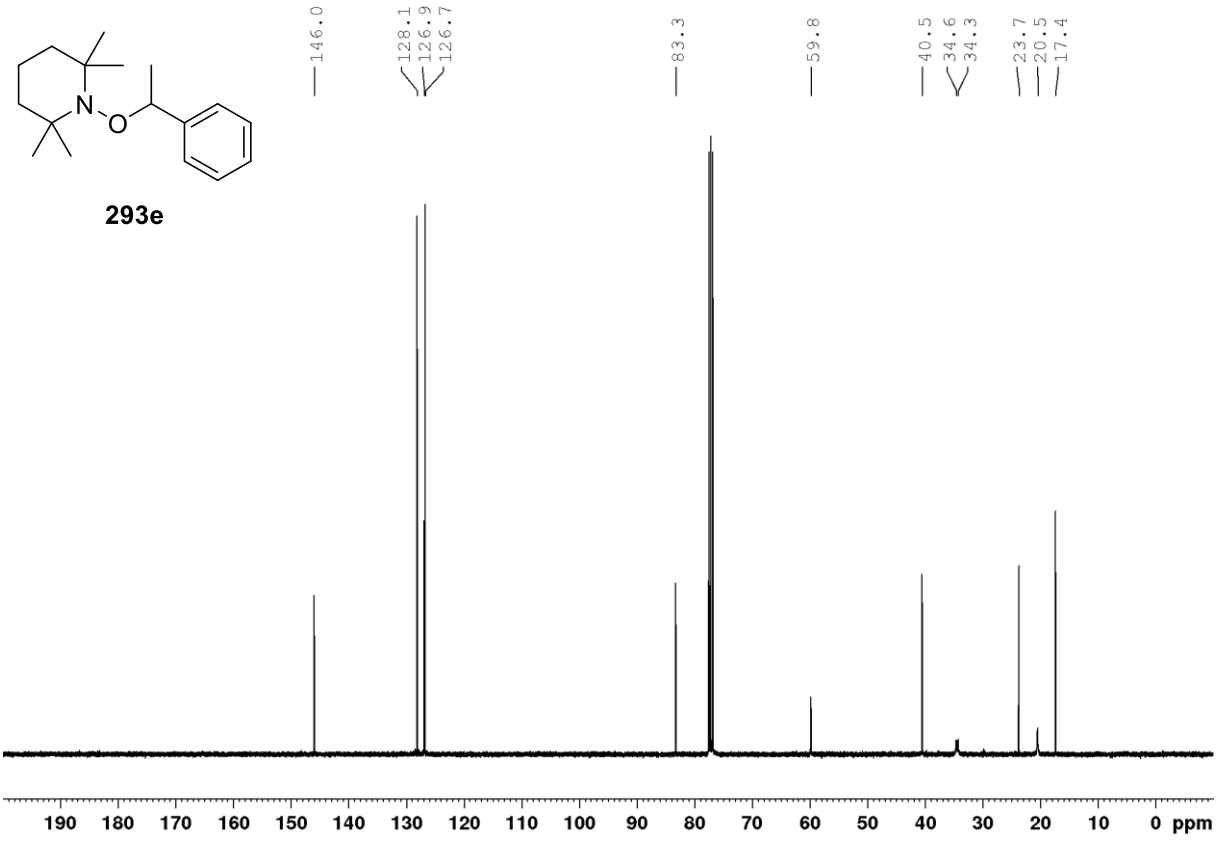


293d



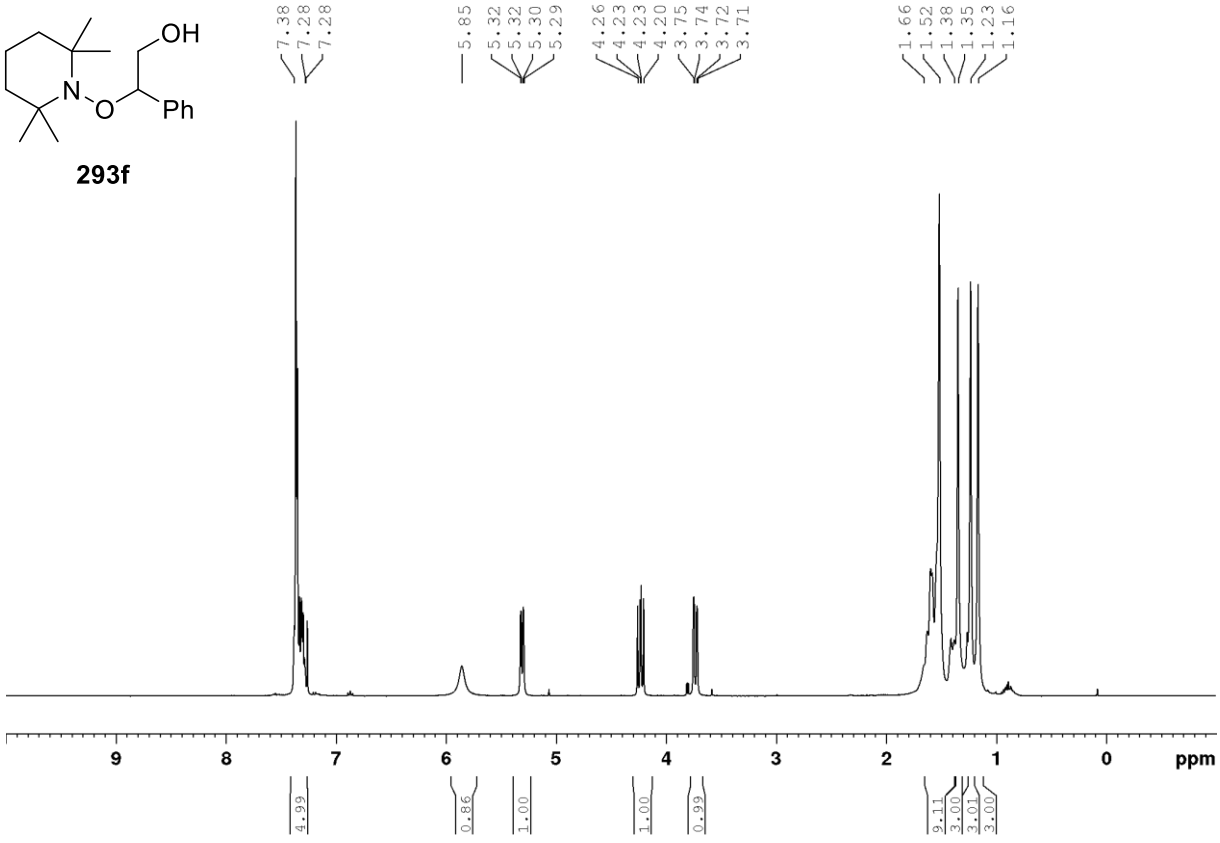
2,2,6,6-Tetramethyl-1-(1-phenylethoxy)piperidine (293e)



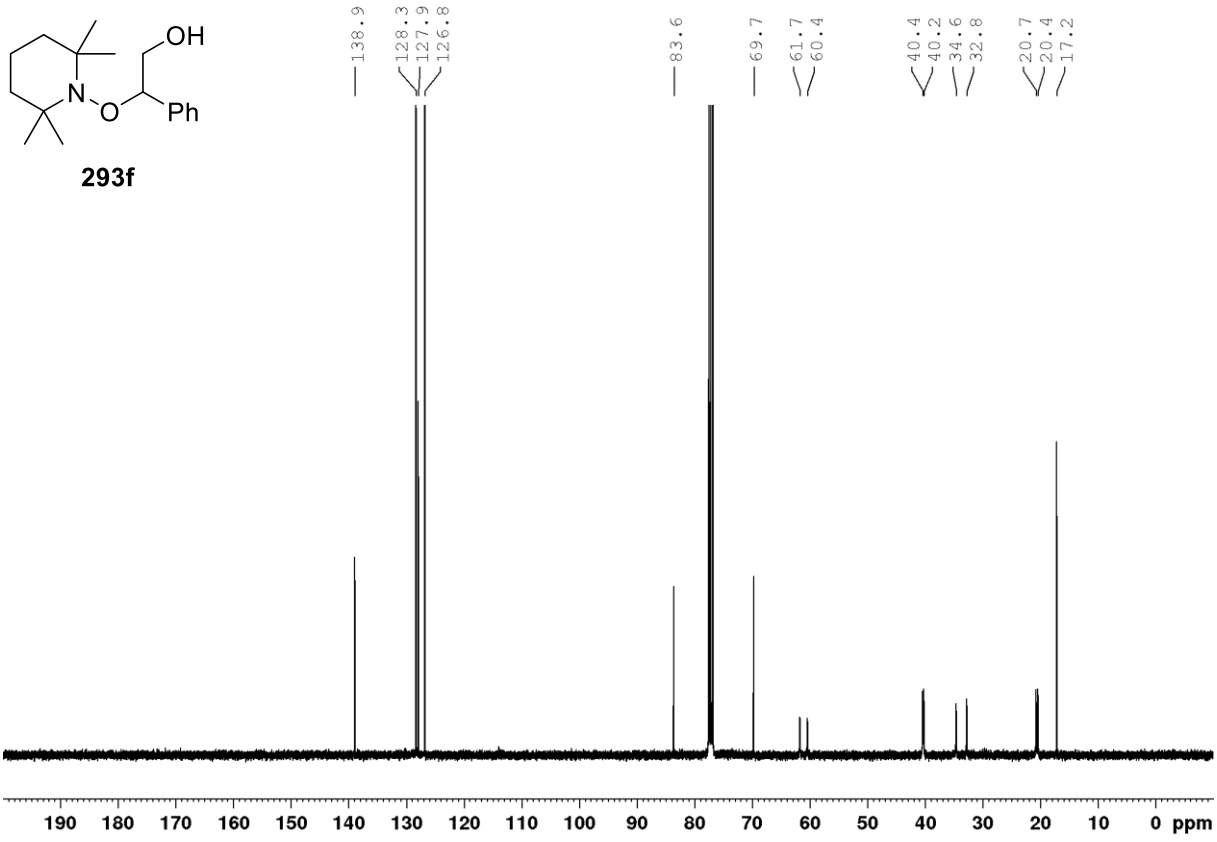


293e

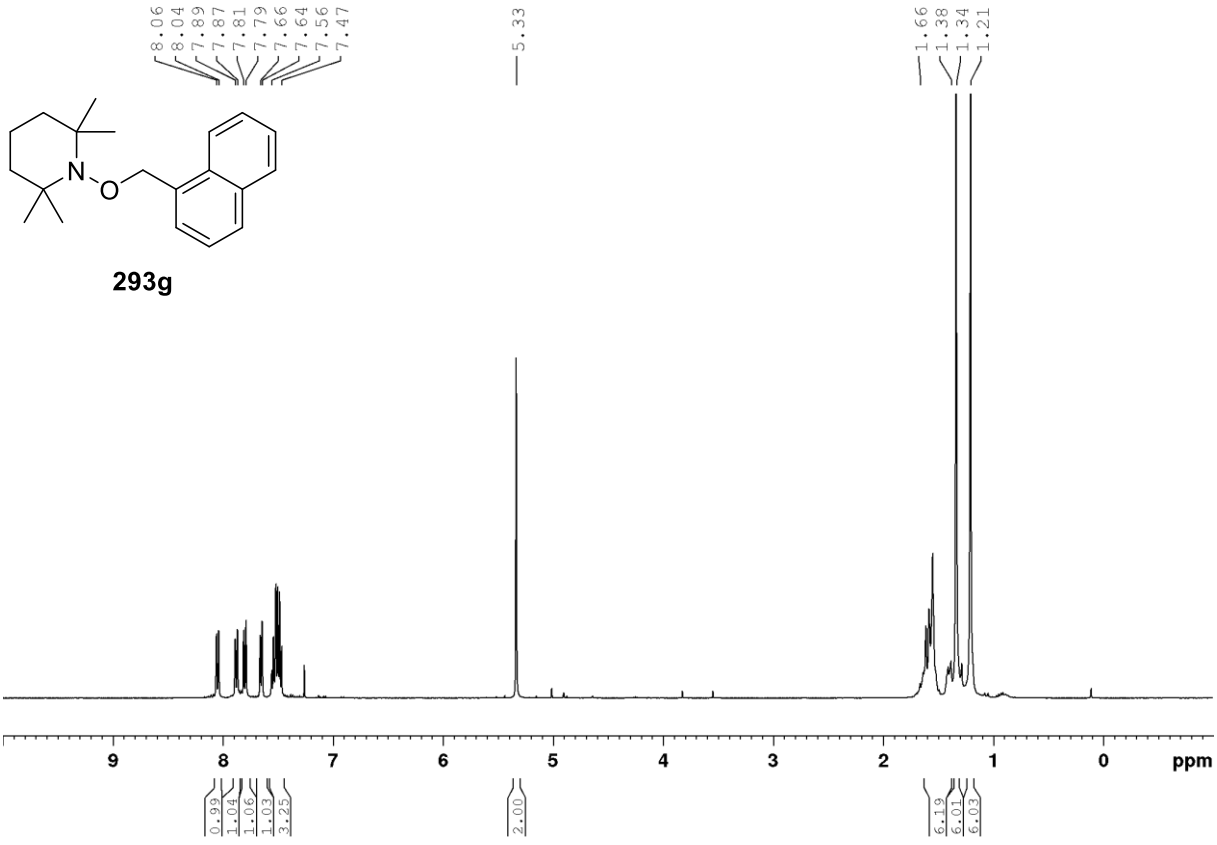
2-Phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethan-1-ol (293f)

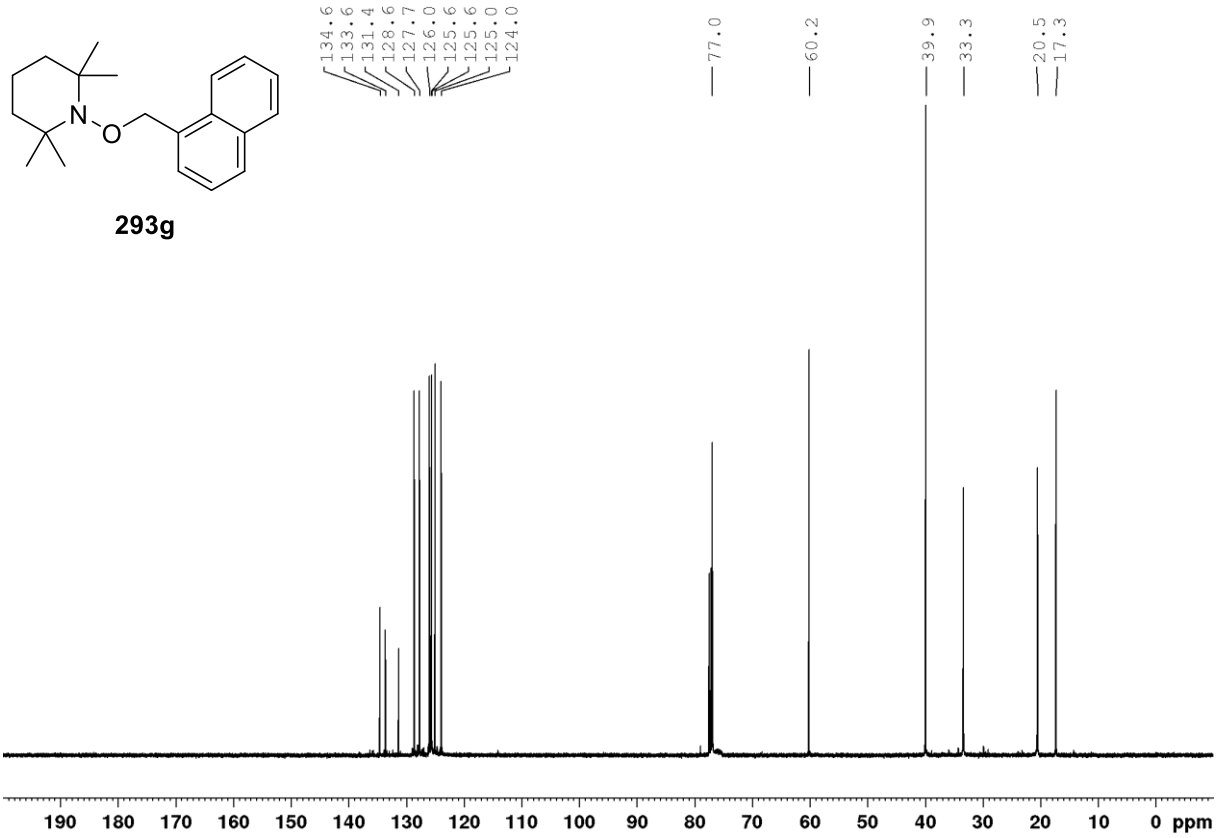


293f



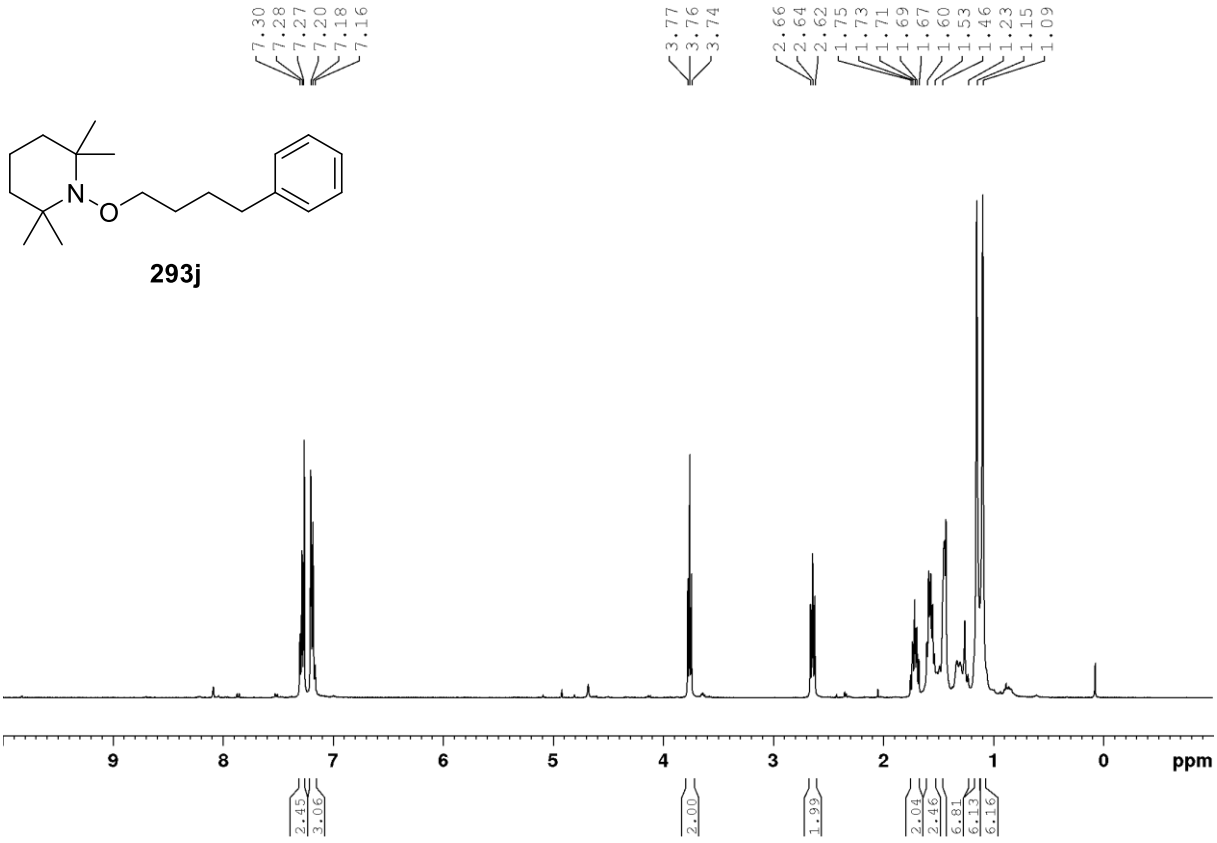
2,2,6,6-Tetramethyl-1-(naphthalen-1-ylmethoxy)piperidine (293g)



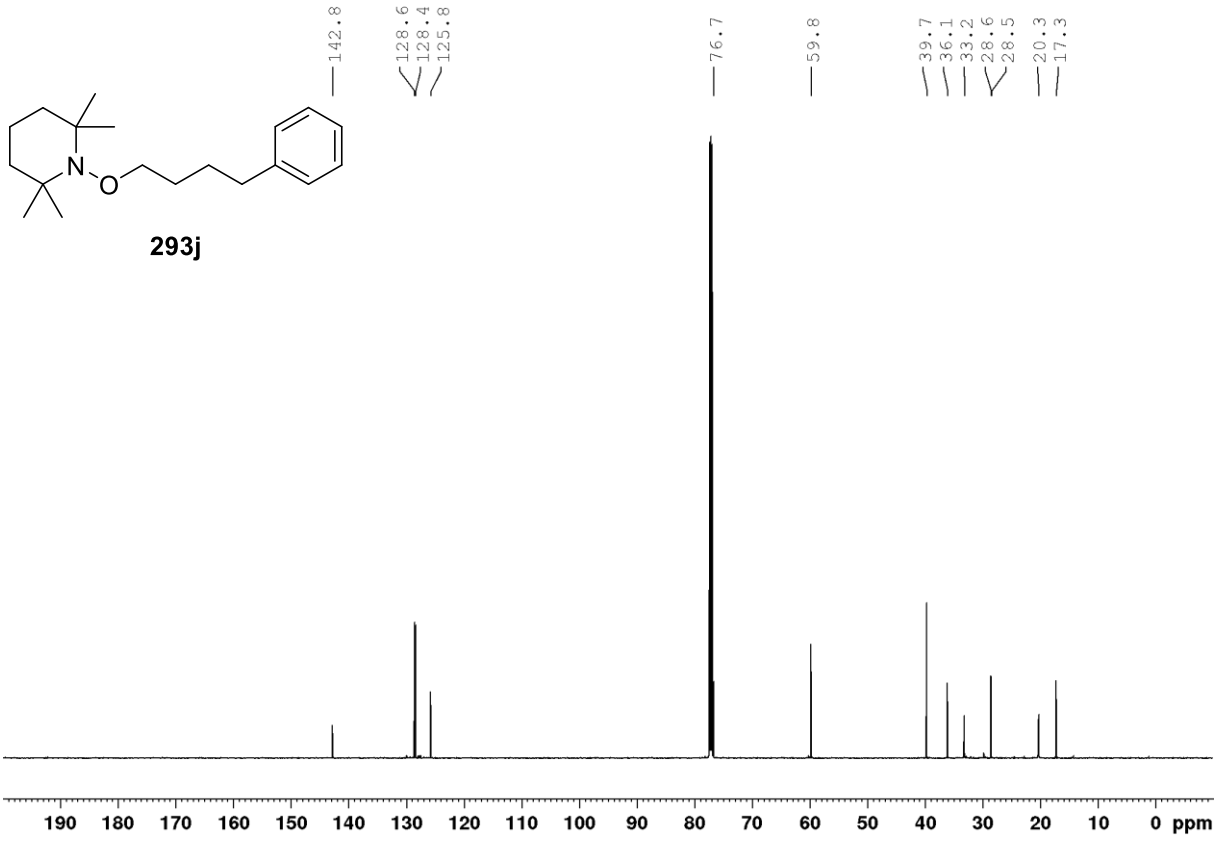


293g

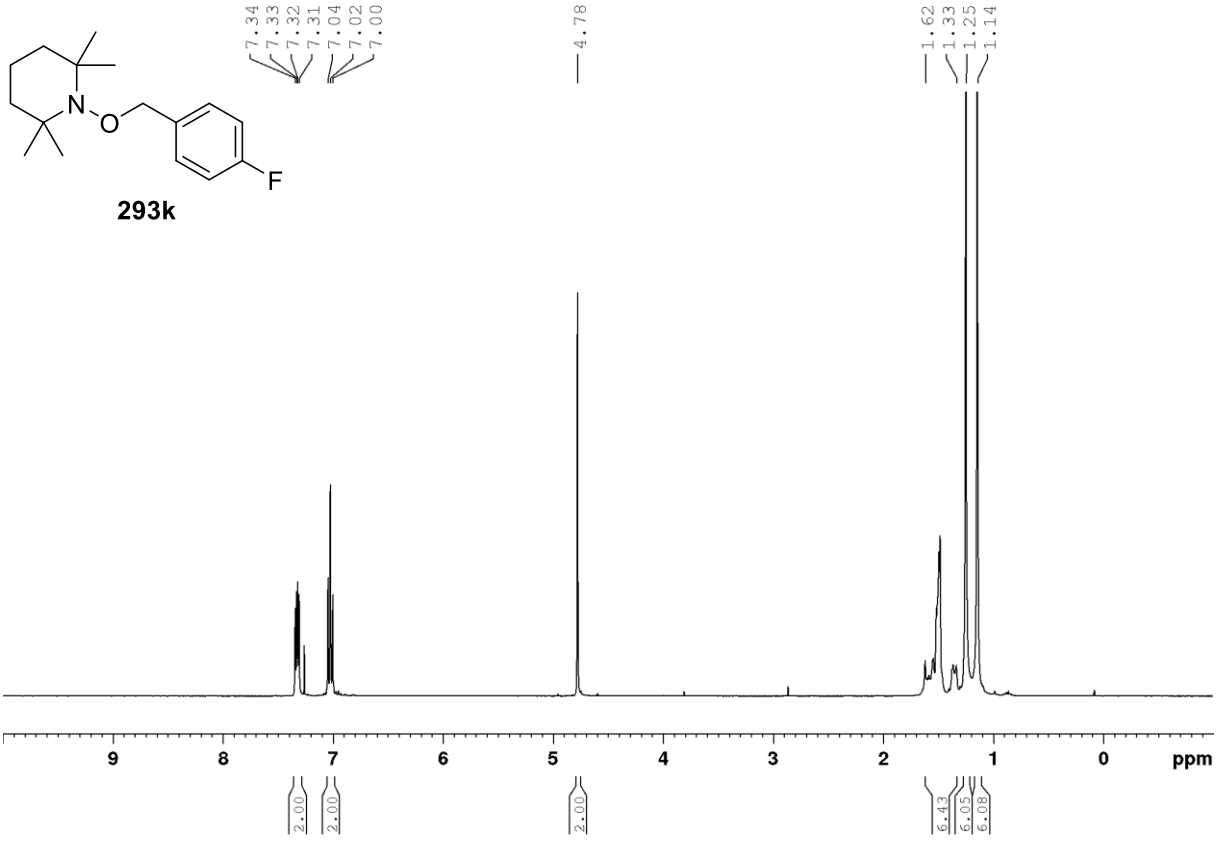
2,2,6,6-Tetramethyl-1-(4-phenylbutoxy)piperidine (293j)

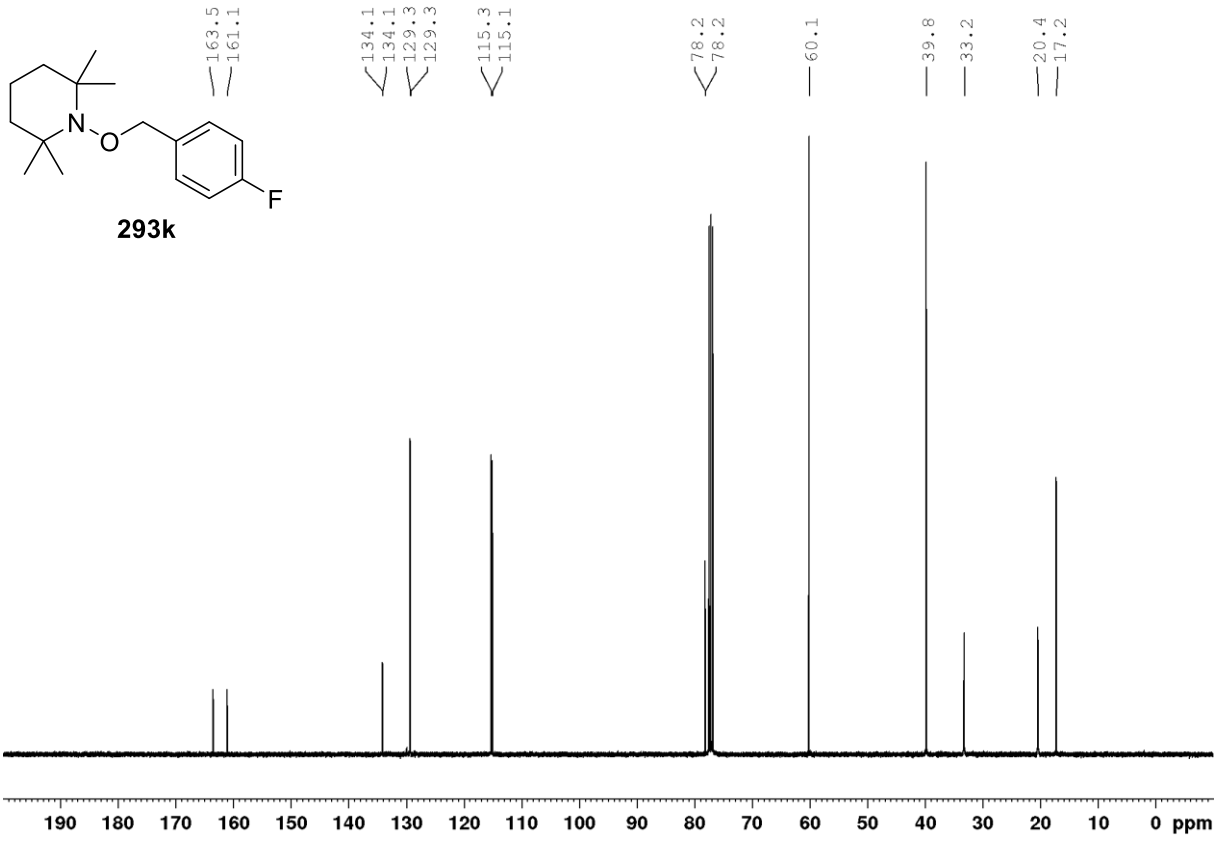


293j

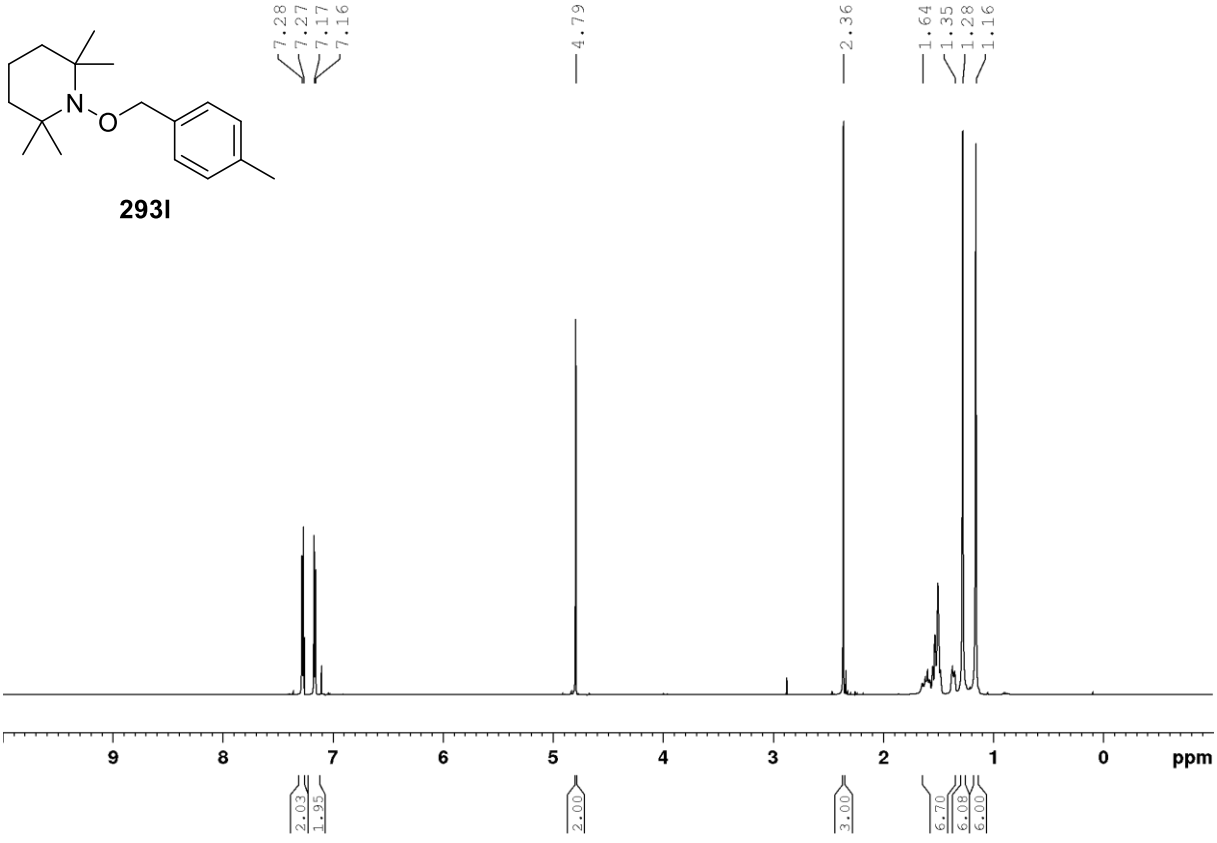


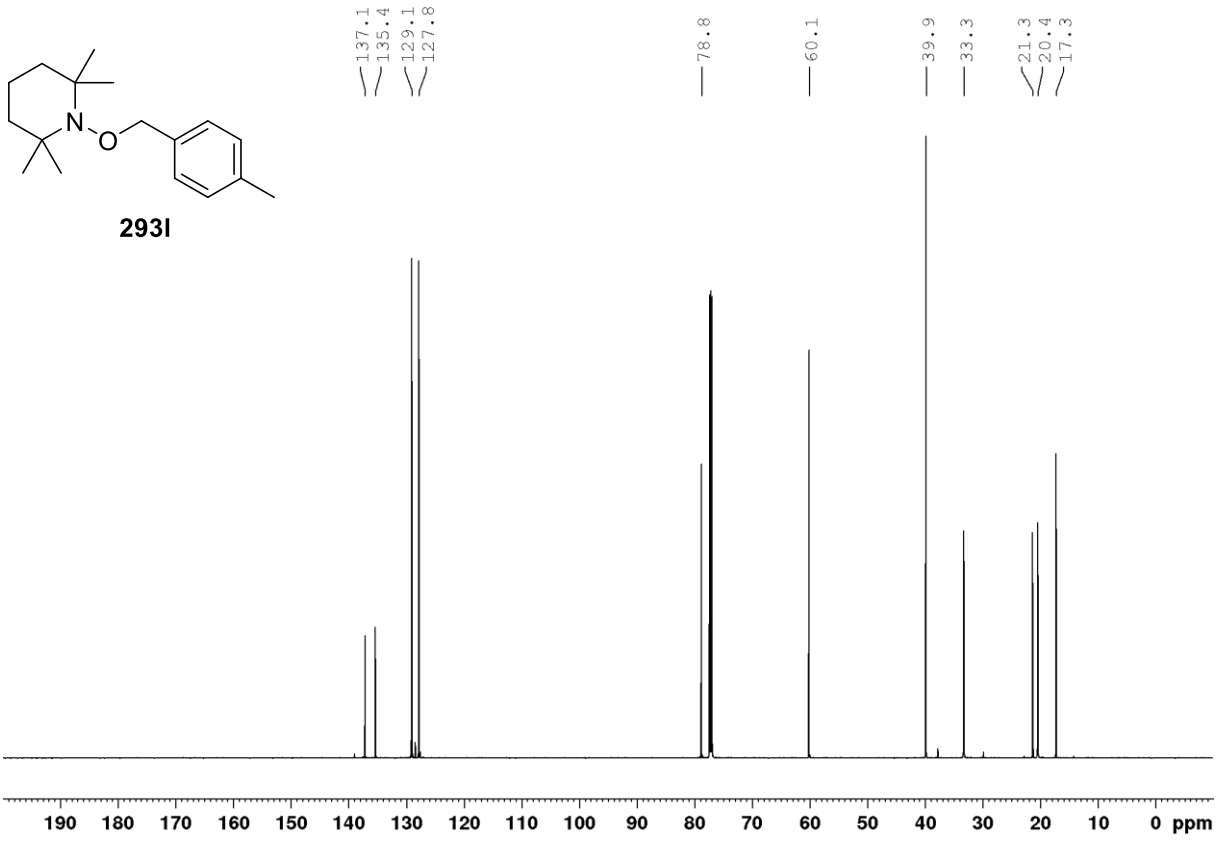
1-((4-Fluorobenzyl)oxy)-2,2,6,6-tetramethylpiperidine (293k)





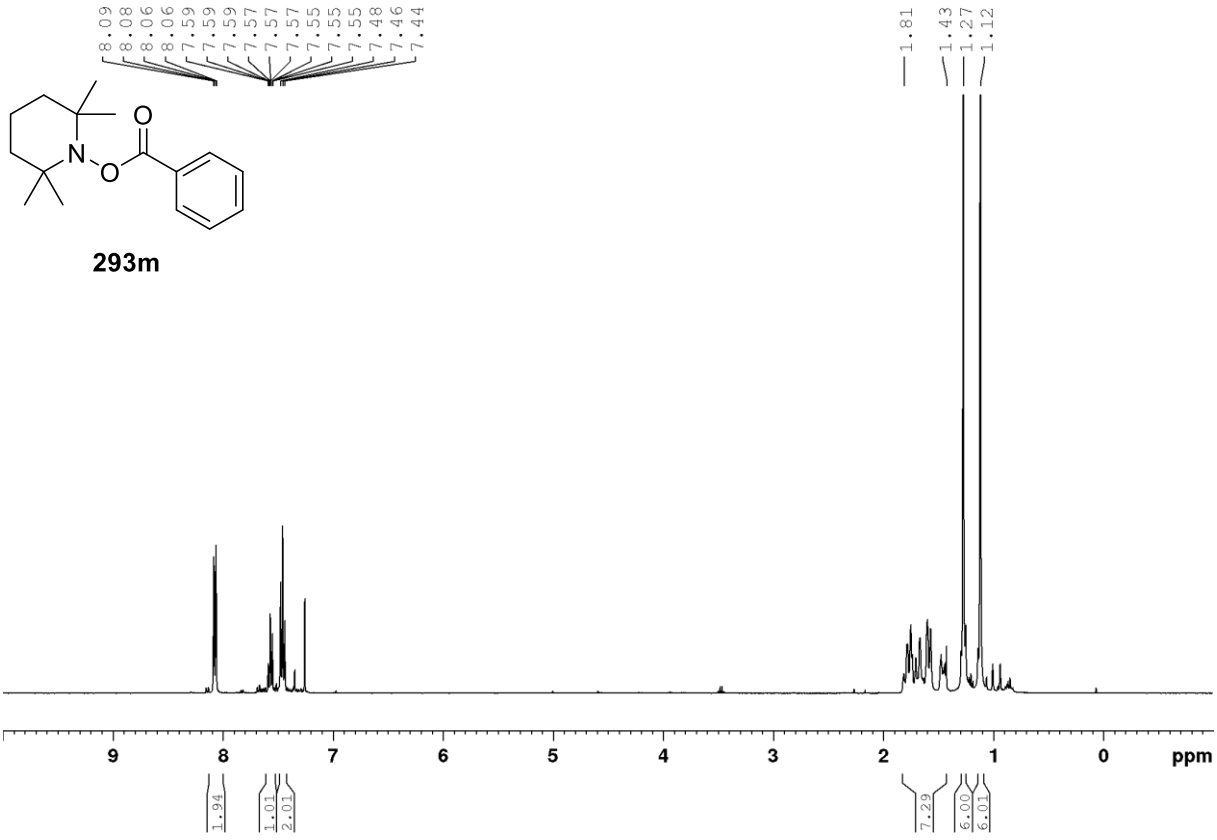
2,2,6,6-Tetramethyl-1-((4-methylbenzy l)oxy)piperidine (293l)



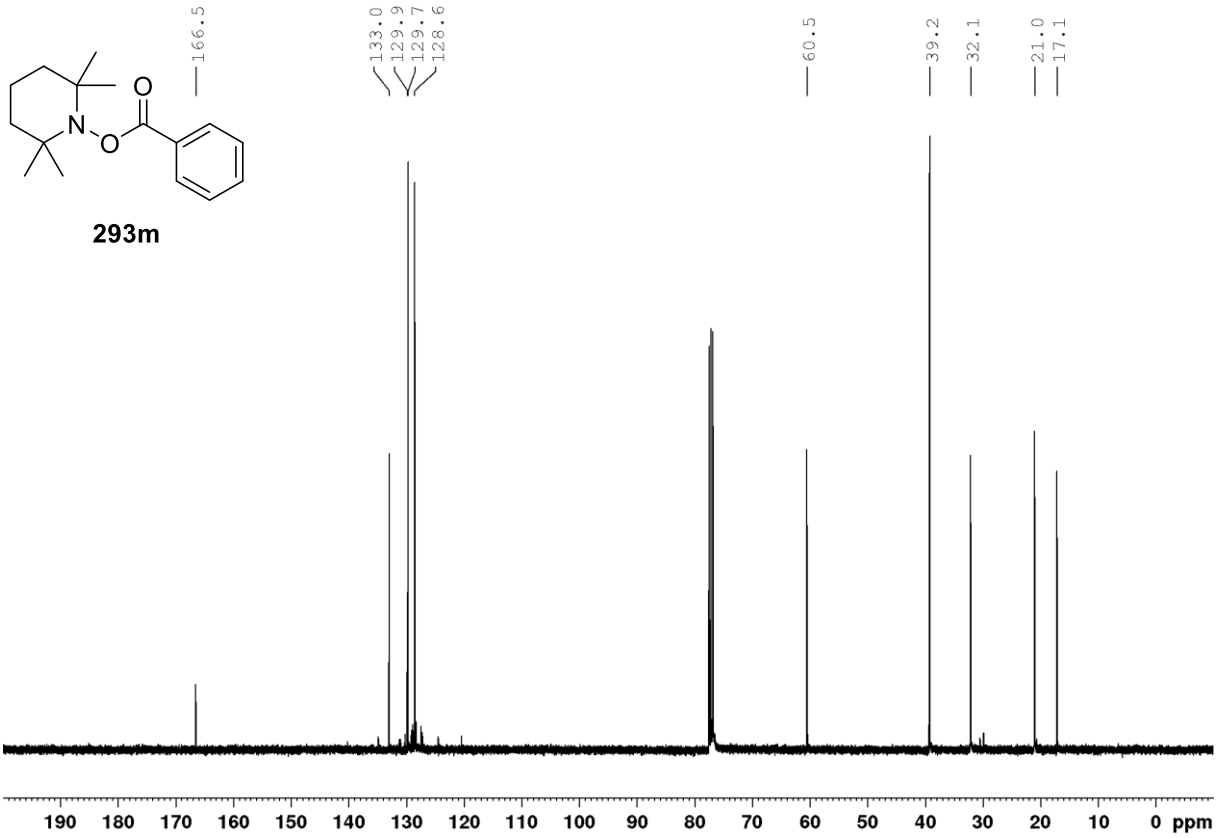


293l

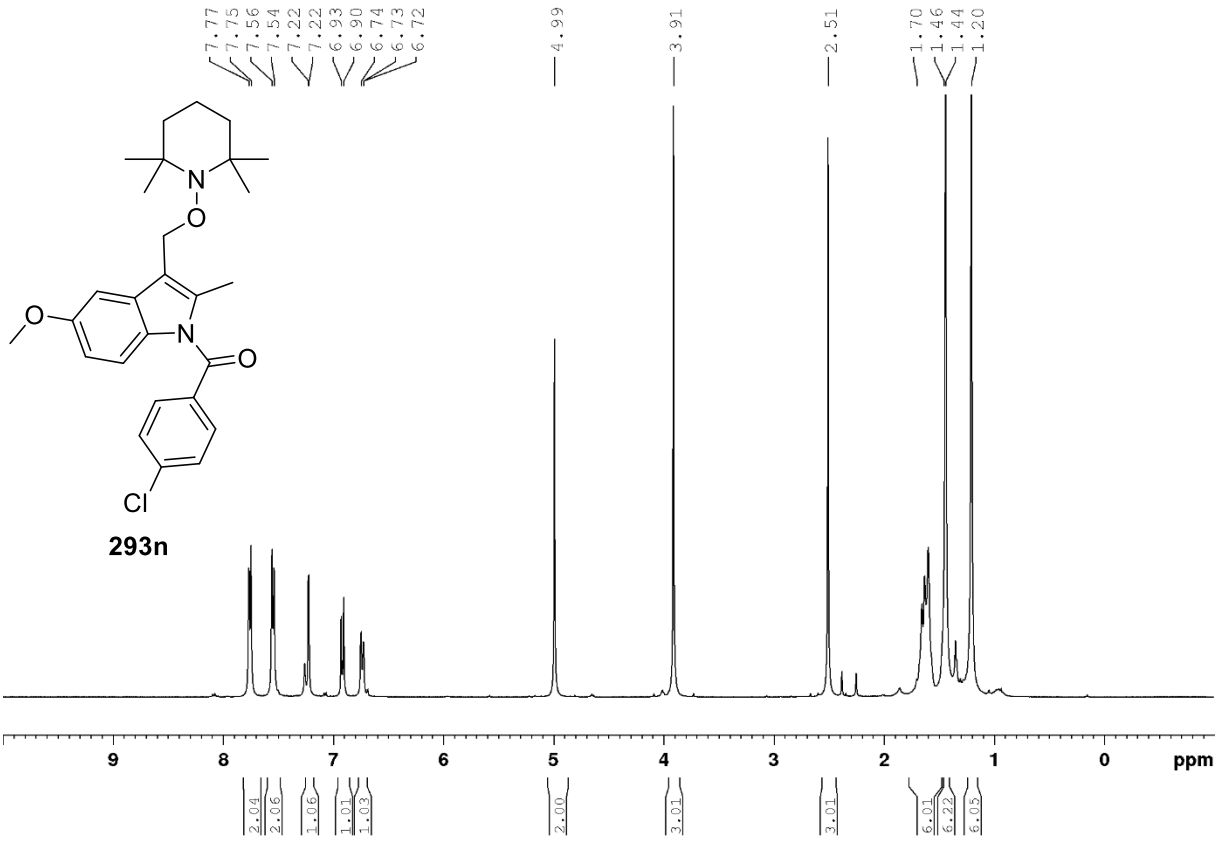
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (293m)

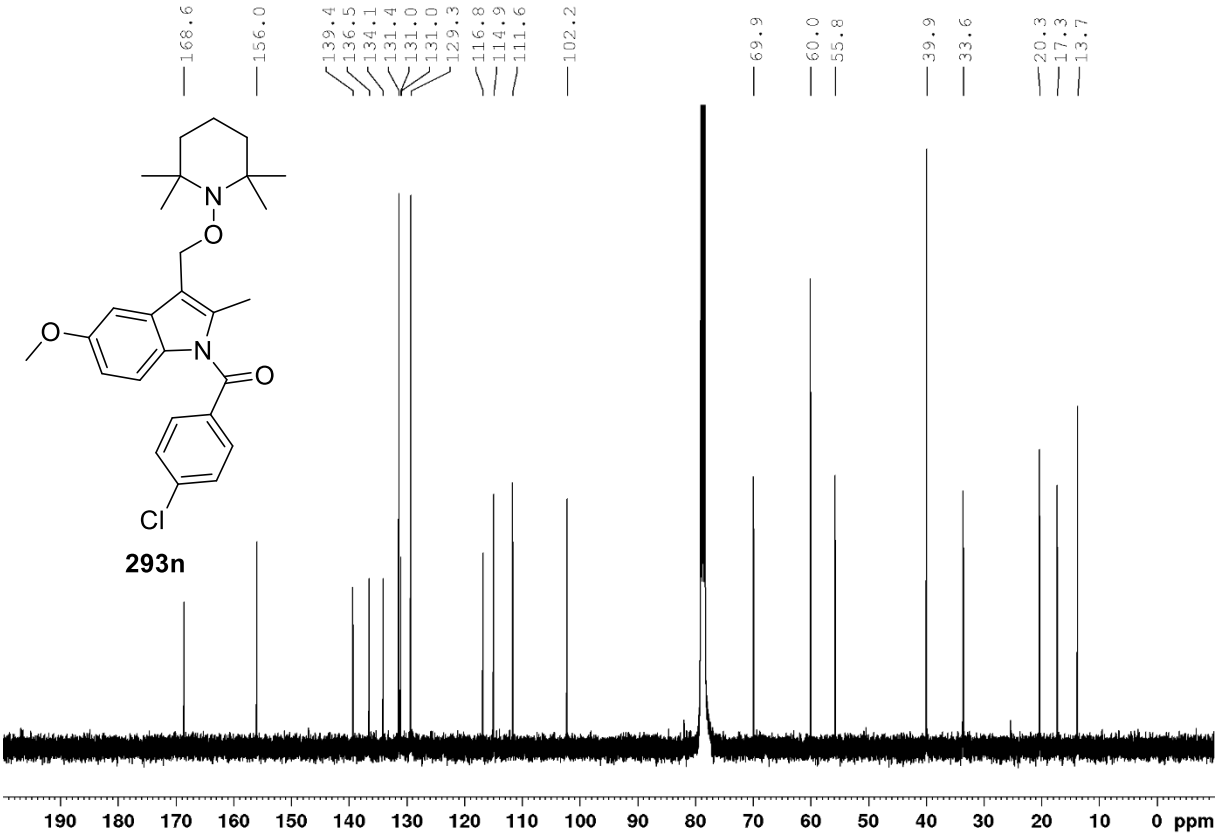


293m

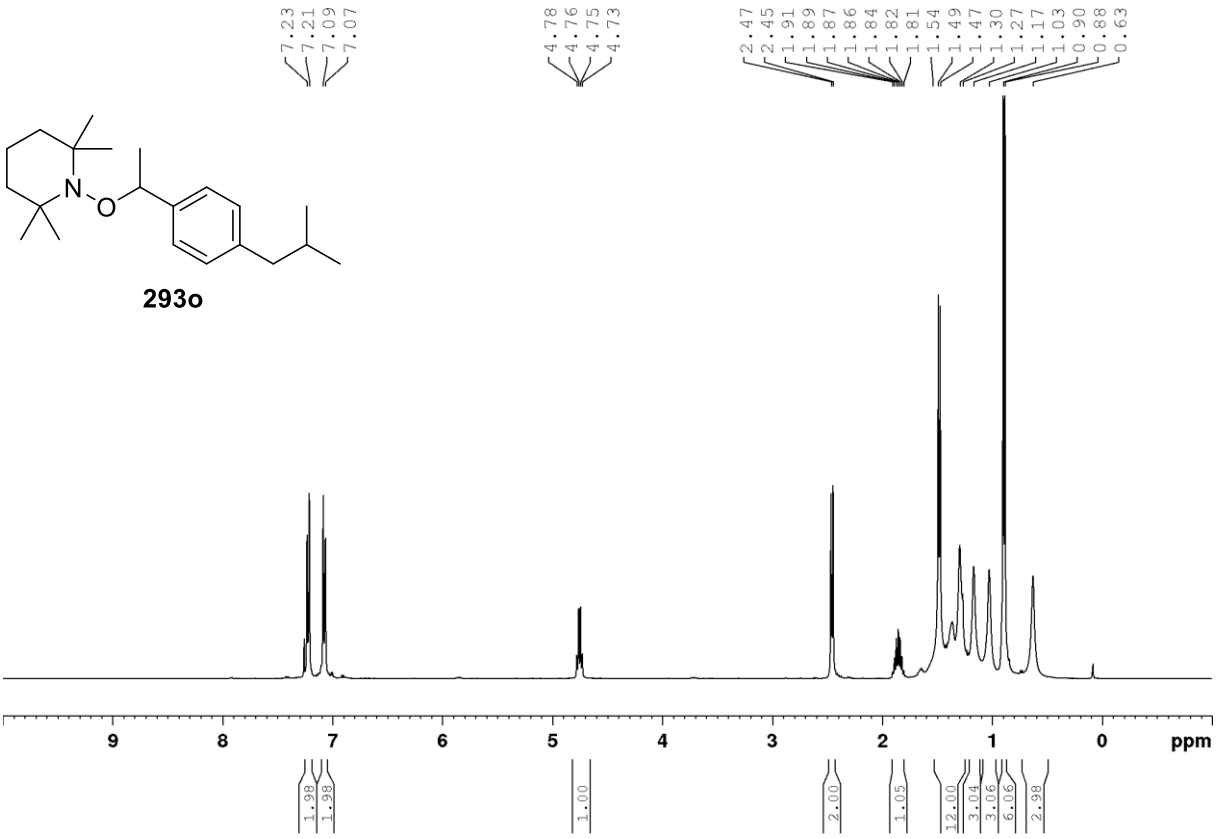


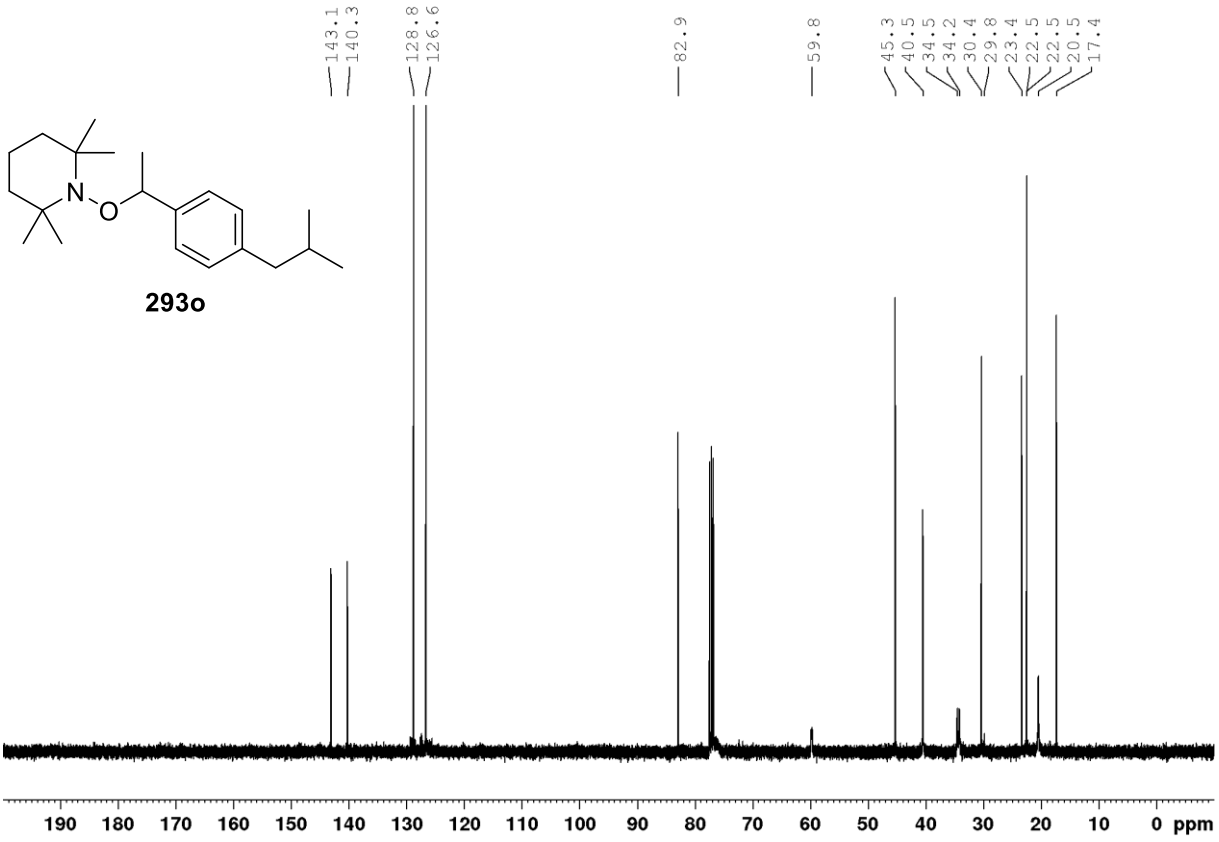
(4-Chlorophenyl)(5-methoxy-2-methyl-3-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-1*H*-indol-1-yl)methanone (293n)



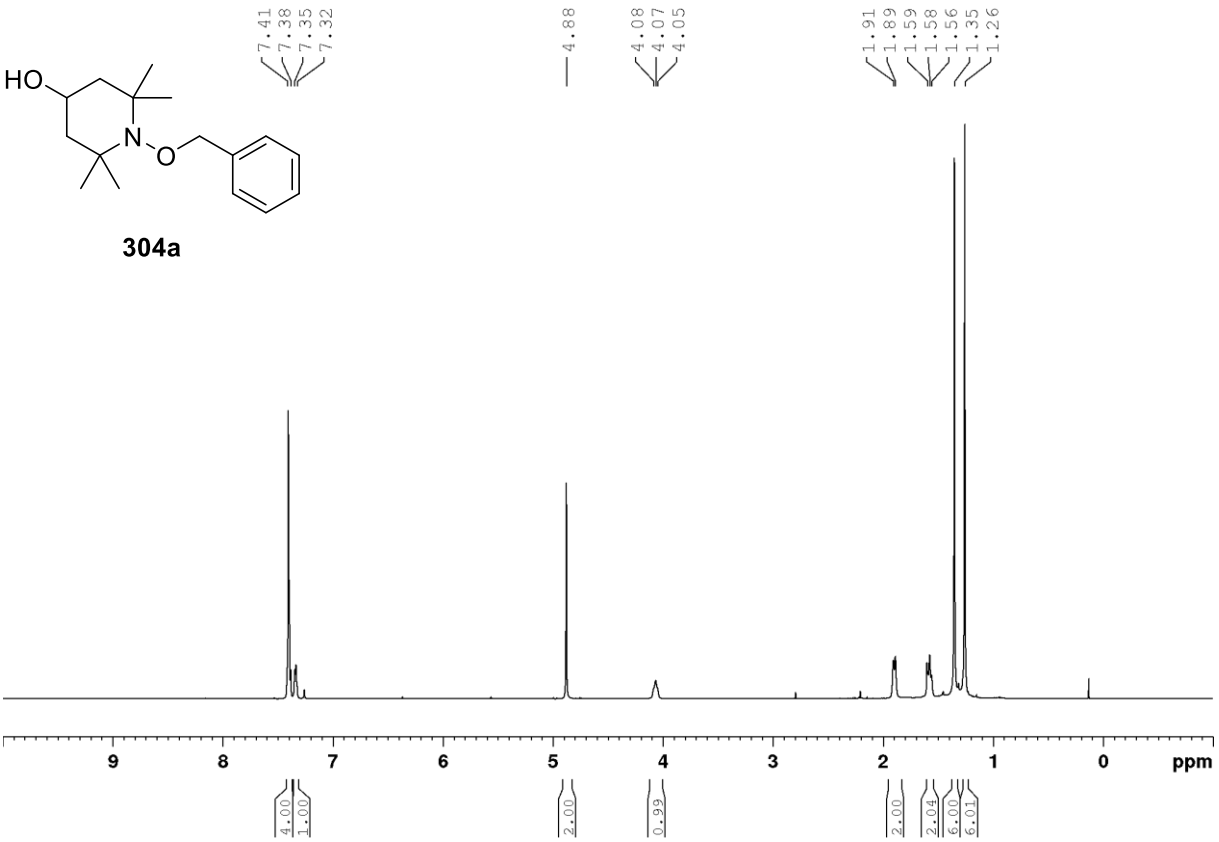


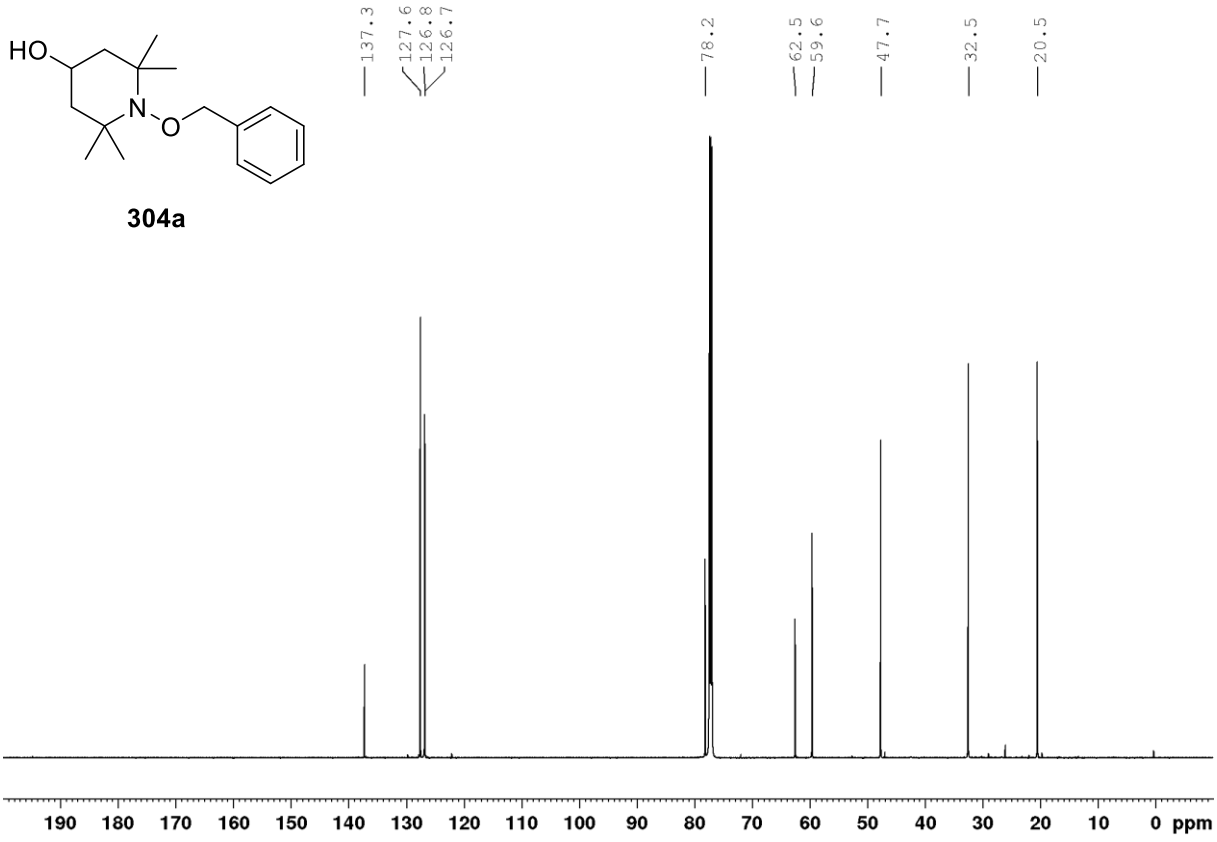
1-(1-(4-Isobutylphenyl)ethoxy)-2,2,6,6-tetramethylpiperidine (293o)



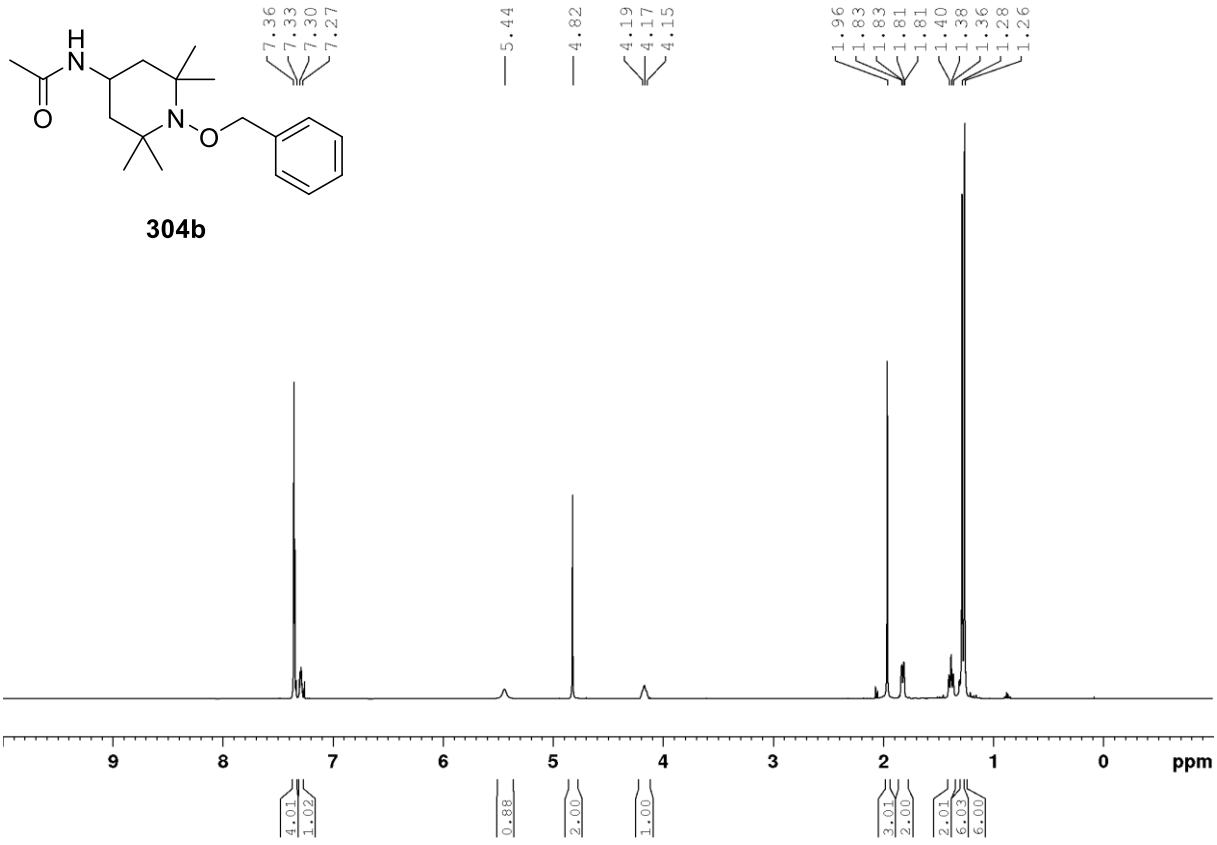


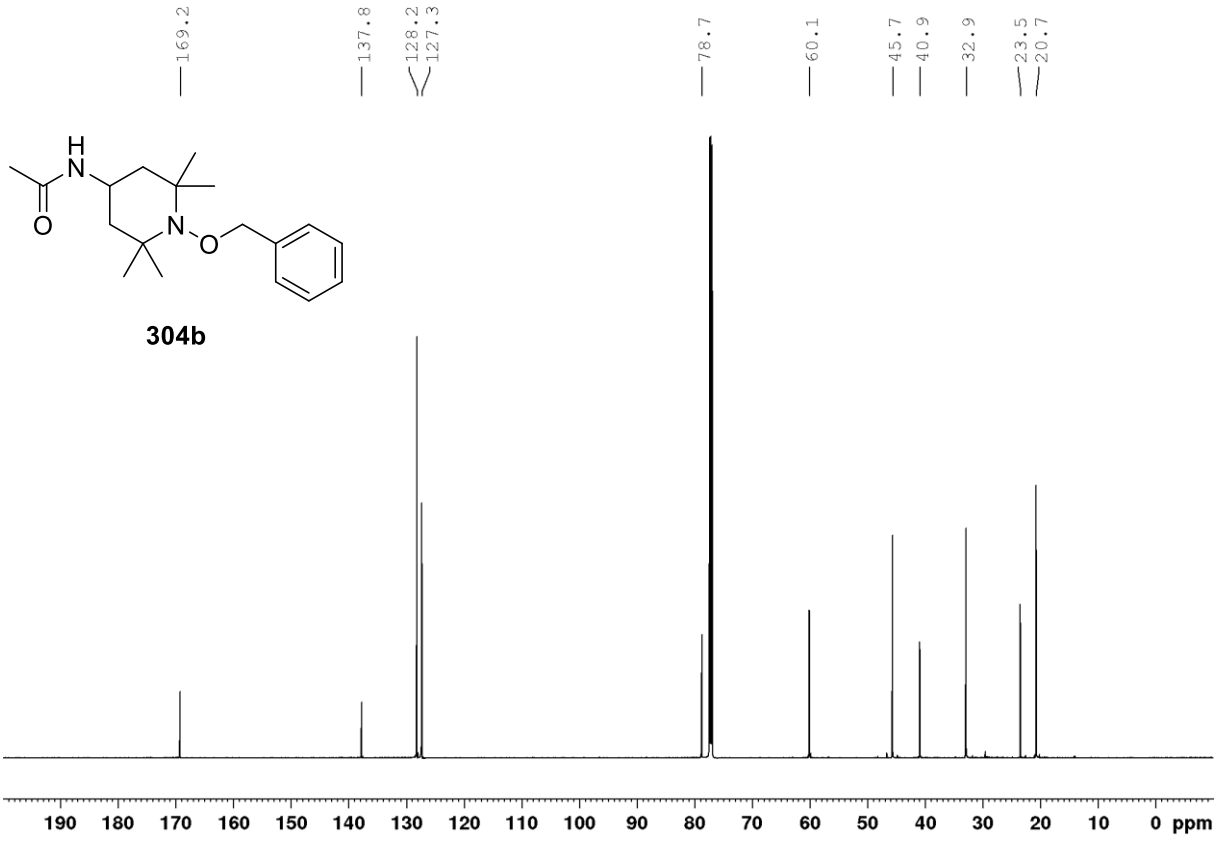
1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-ol (304a)



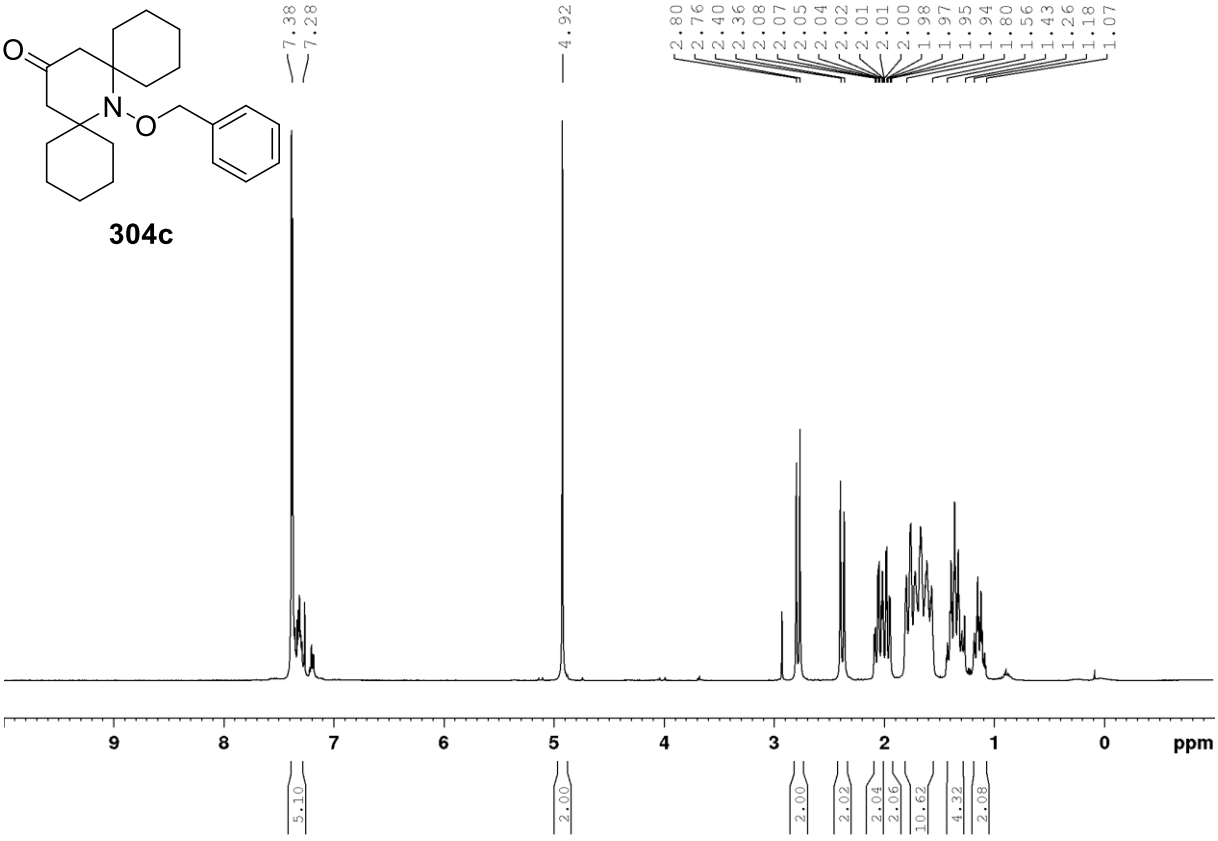


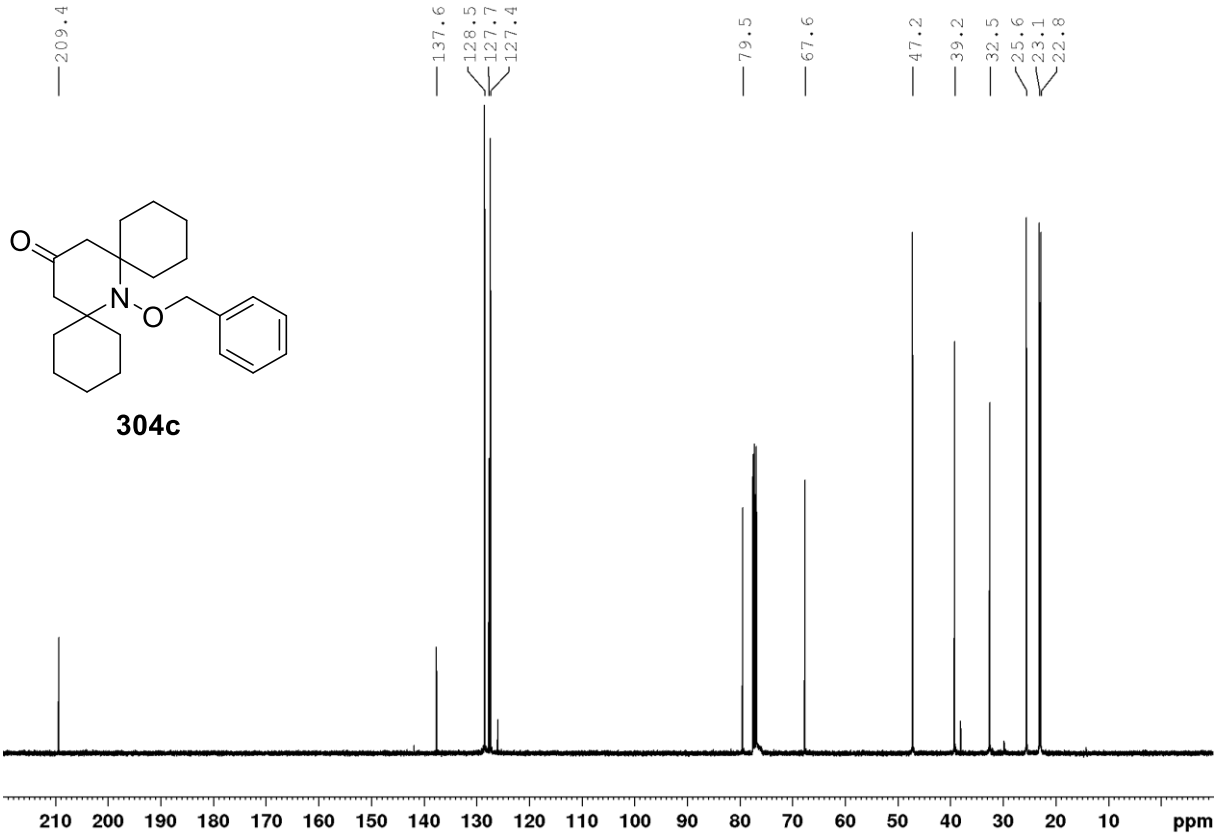
N-(1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-yl)acetamide (304b)



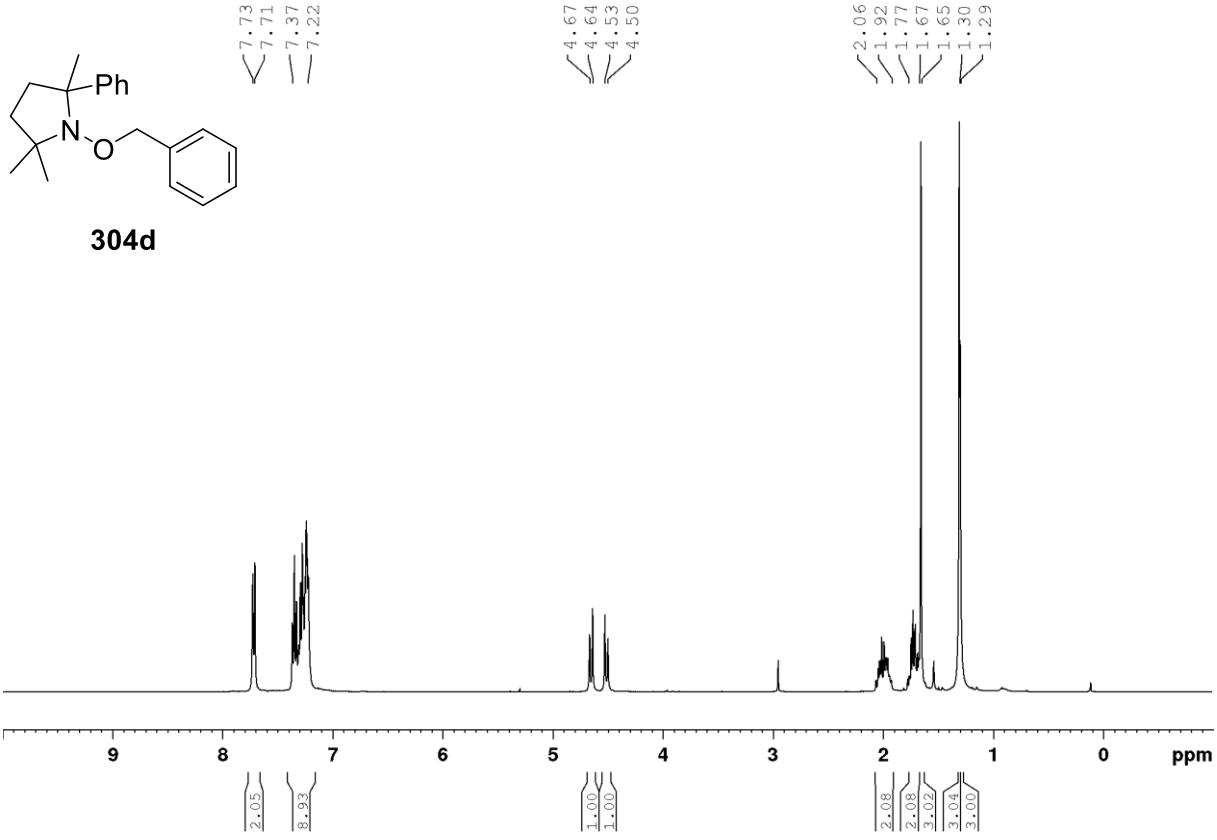


7-(Benzyloxy)-7-azadispiro[5.1.5^{8}.3^{6}]hexadecan-15-one (304c)





1-(Benzyloxy)-2,2,5-trimethyl-5-phenylpyrrolidine (304d)



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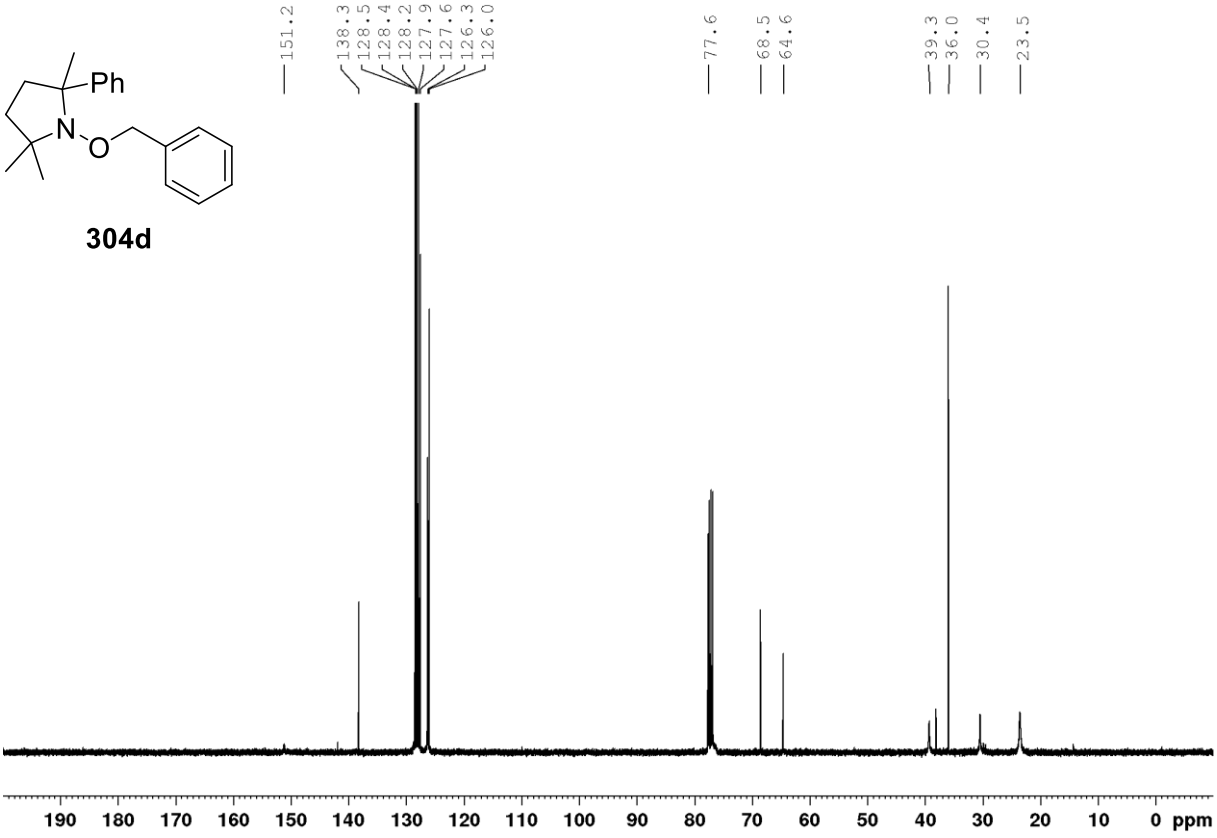
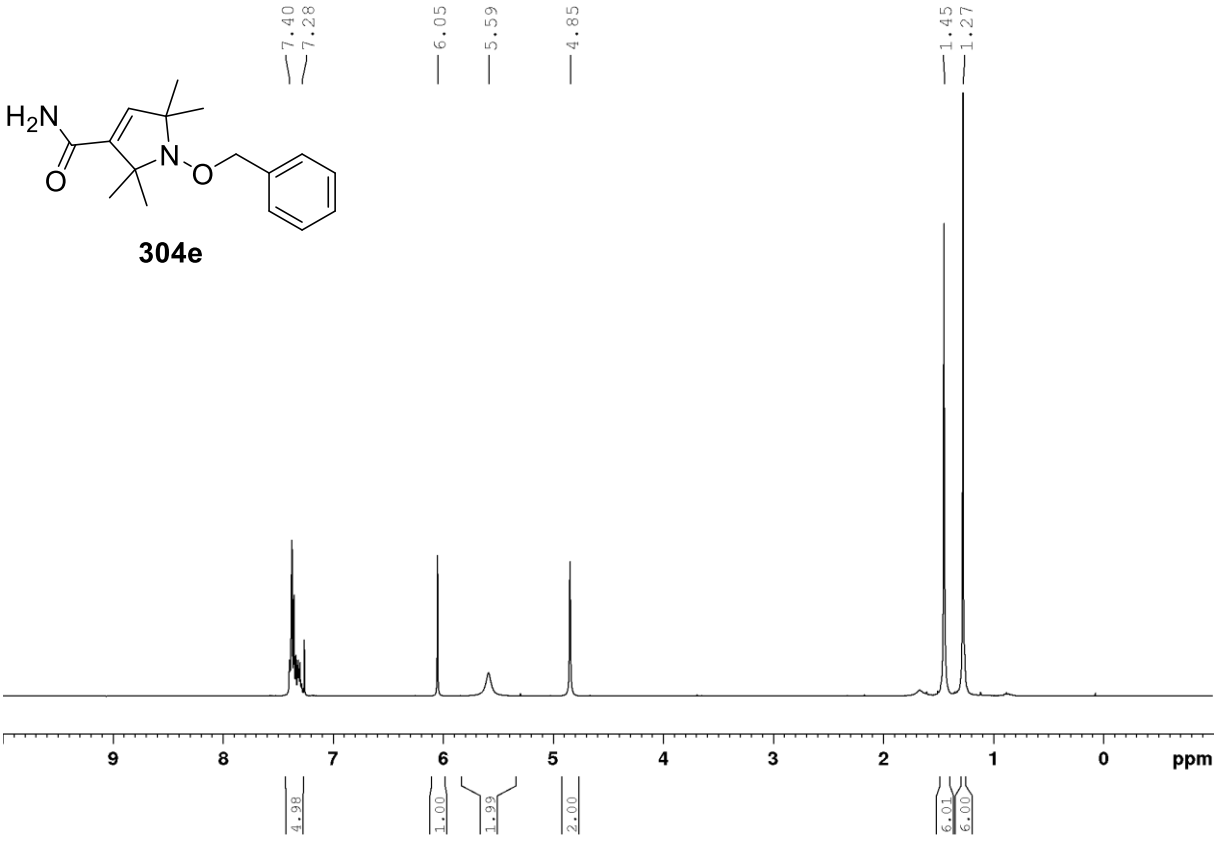
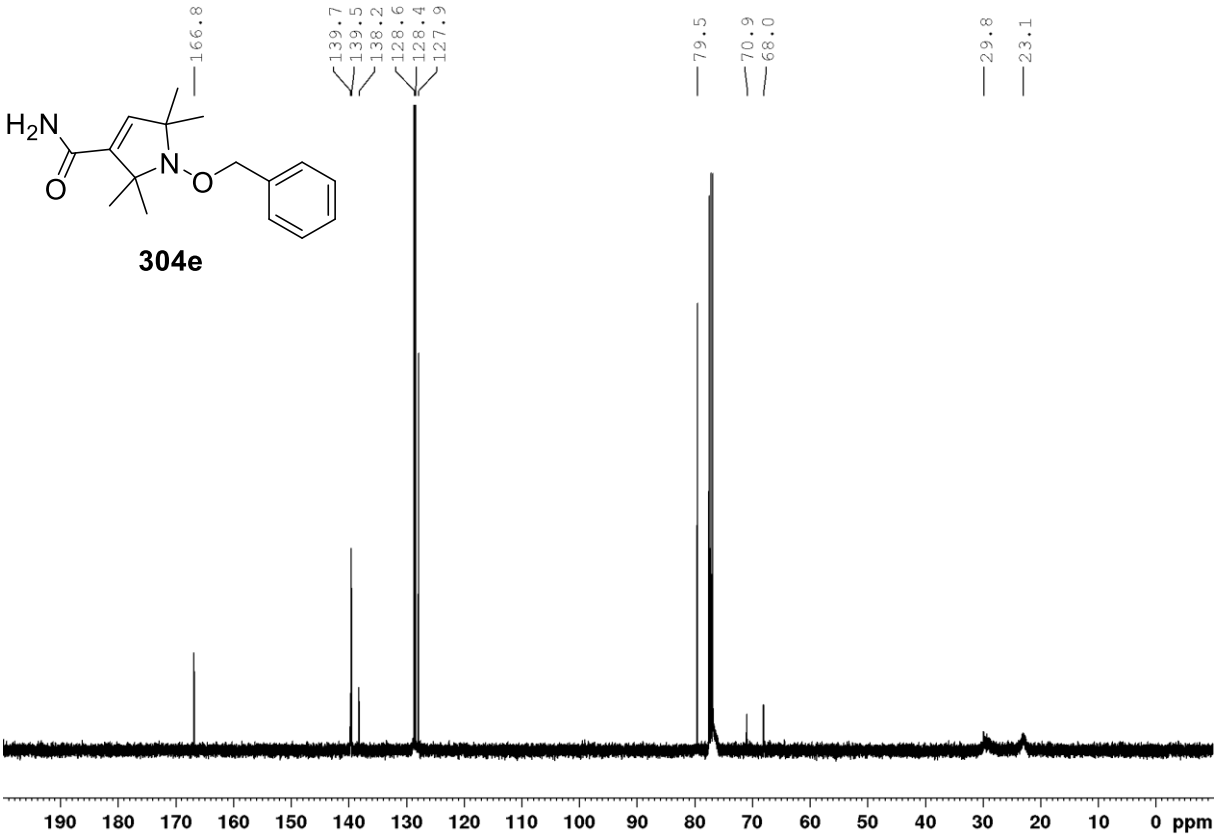


304d

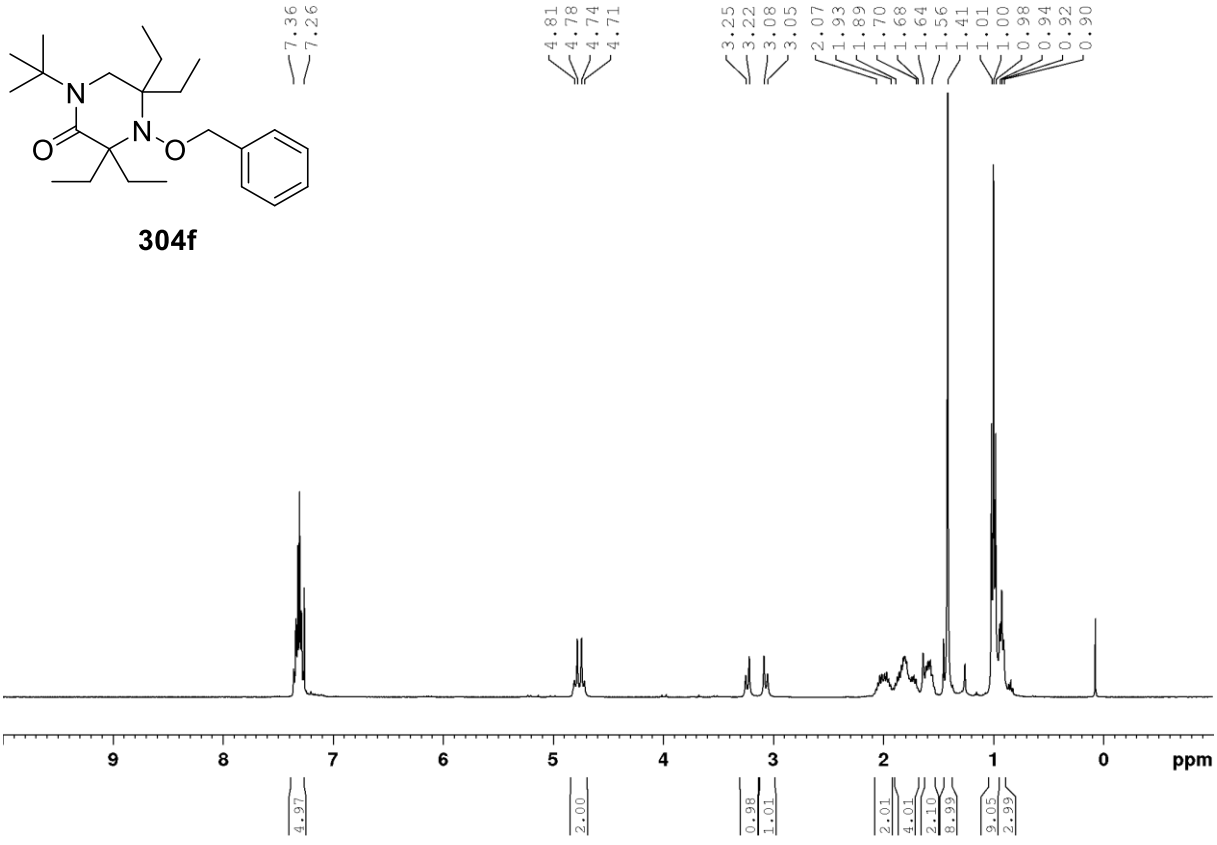
1-(Benzyloxy)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide (304e)

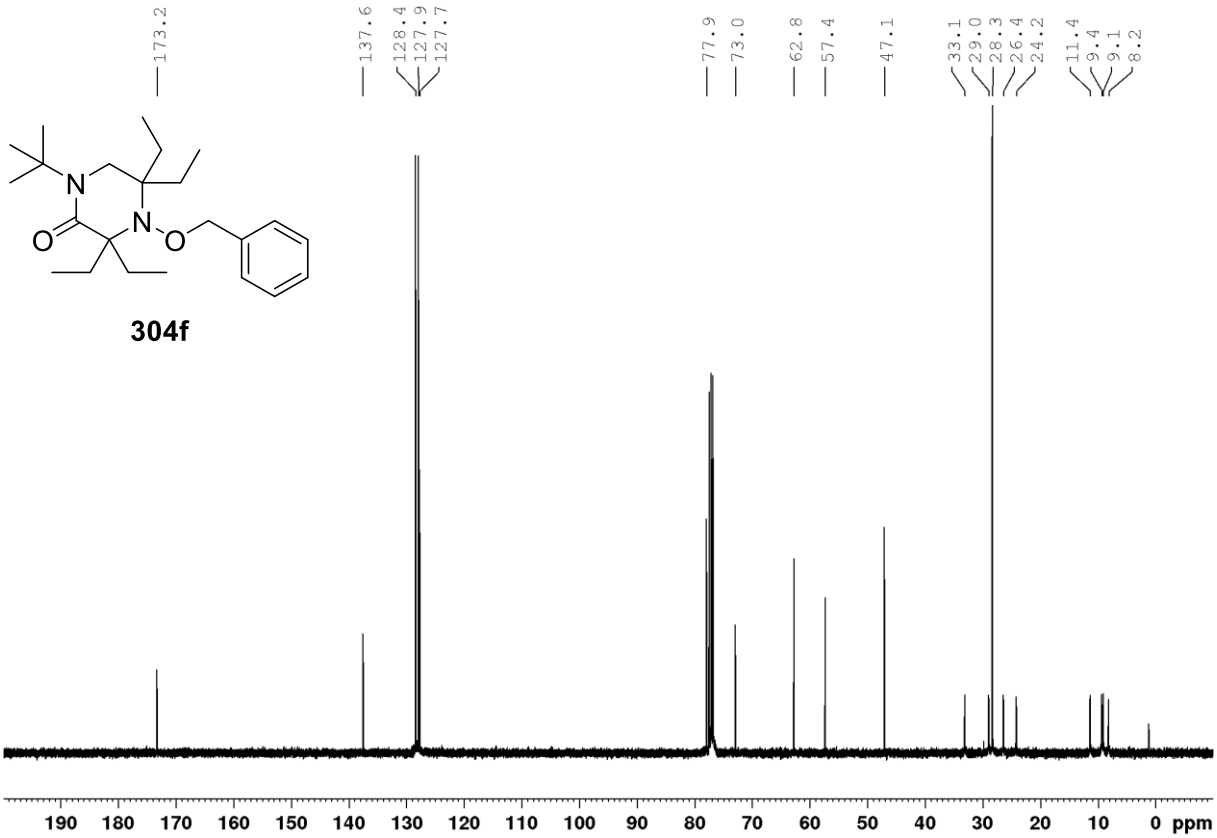


304e

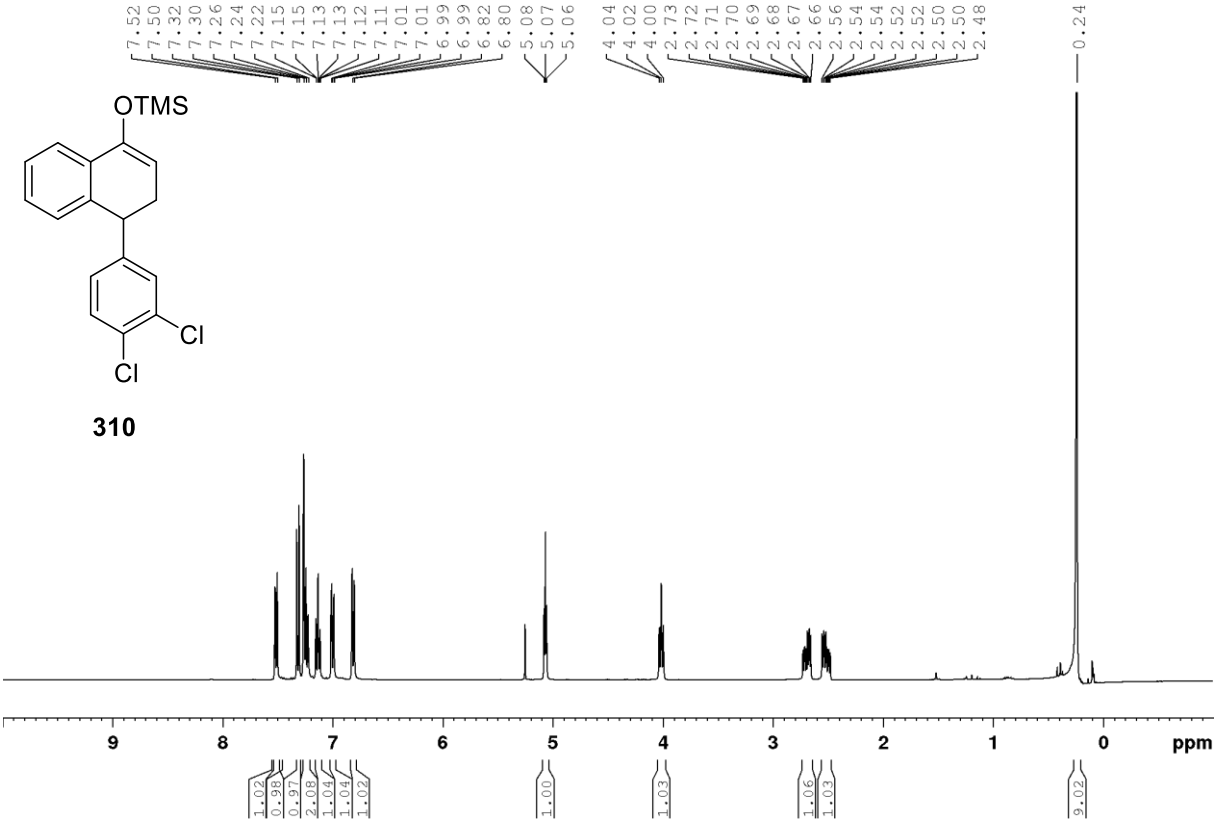


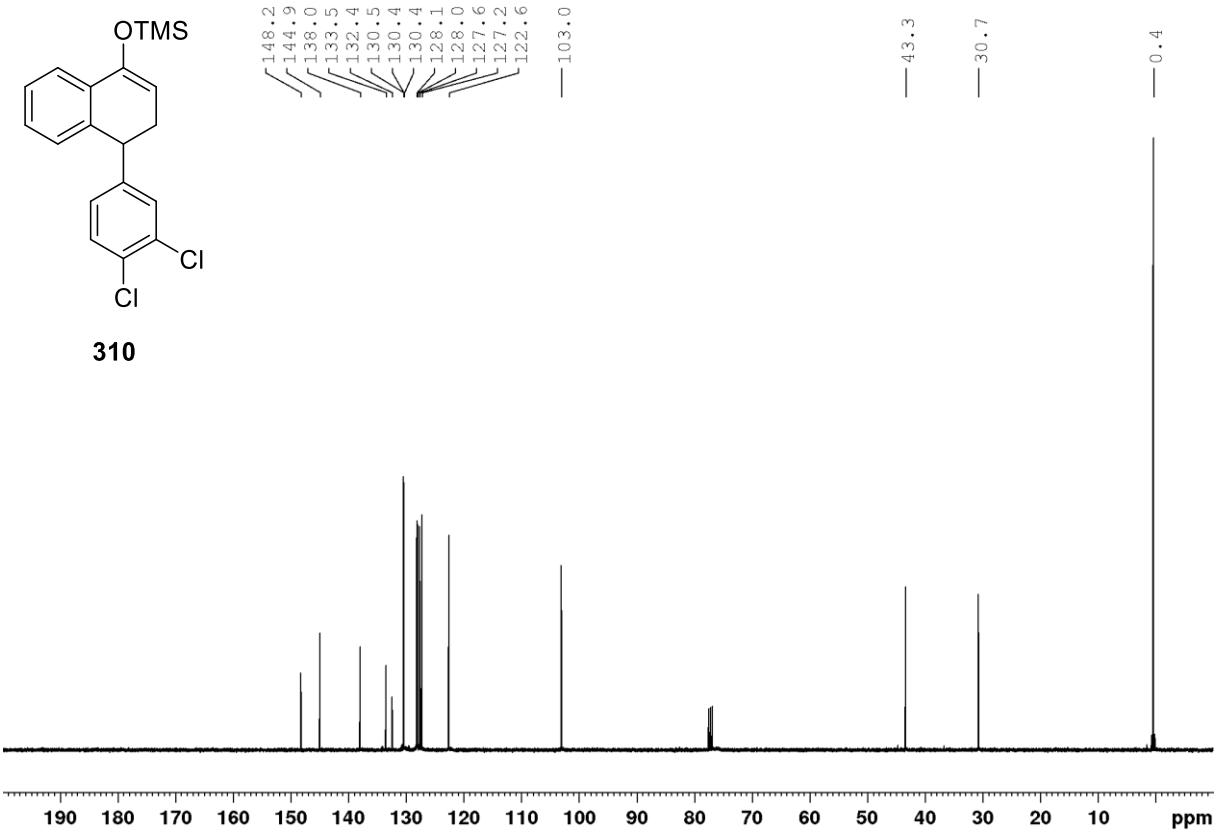
4-(Benzyloxy)-1-(*tert*-butyl)-3,3,5,5-tetraethylpiperazin-2-one (304f)





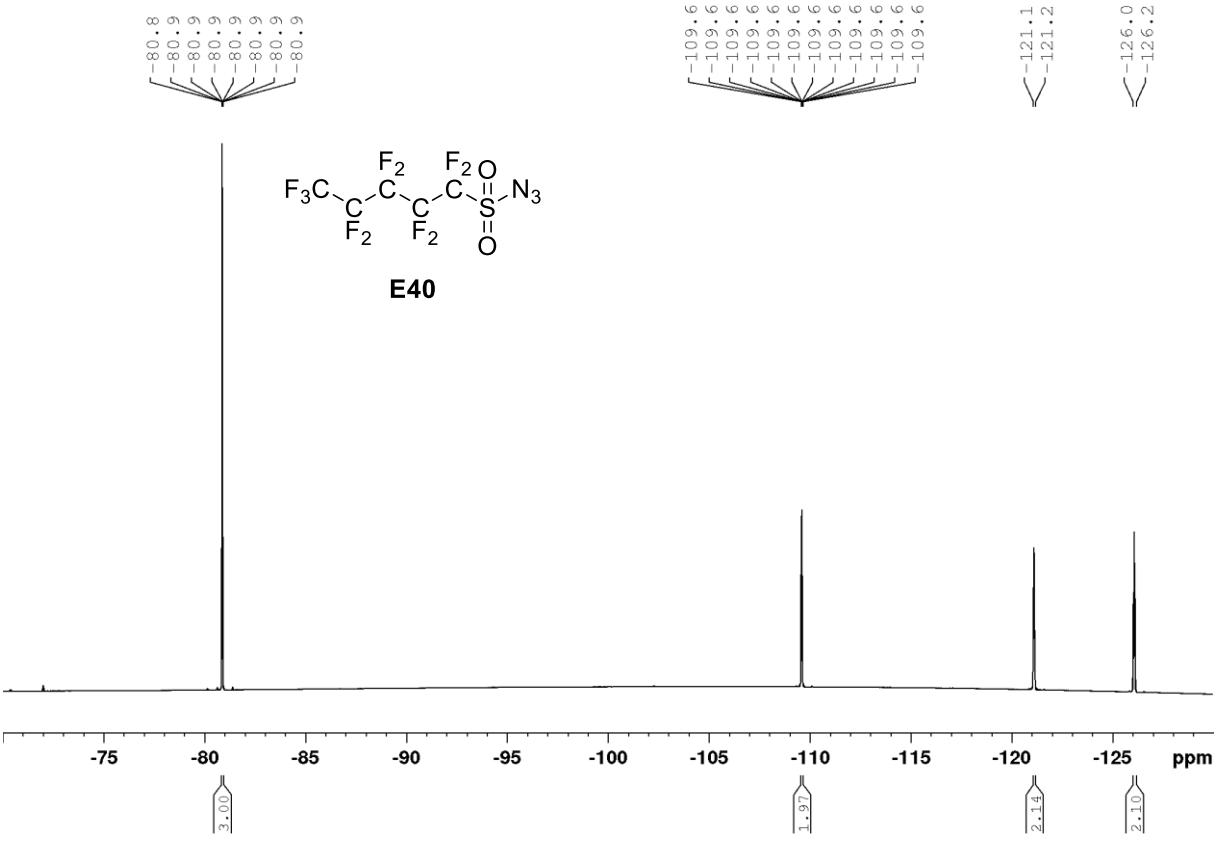
((4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1-yl)oxy)trimethylsilane (310)



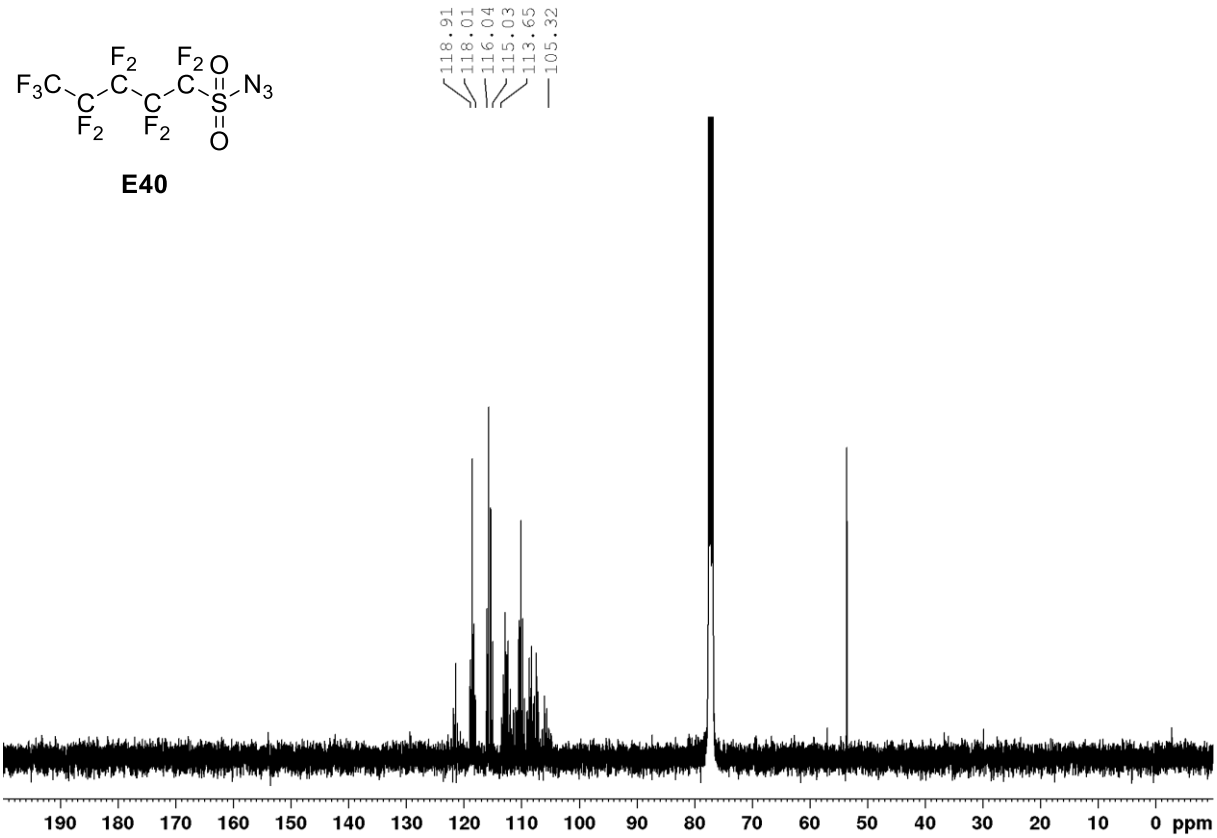


310

1,1,2,2,3,3,4,4,5,5,5-Undecafluoropentane-1-sulfonyl azide (E40)

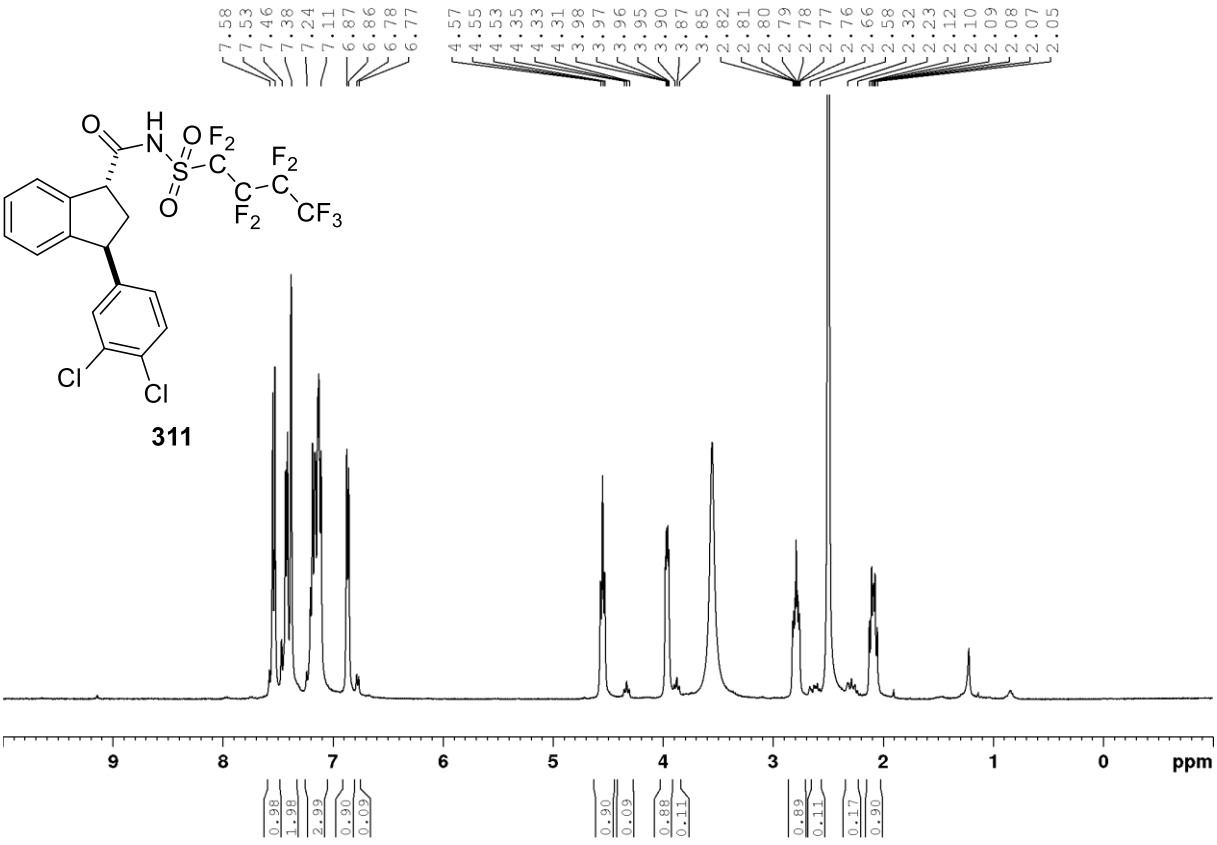


E40

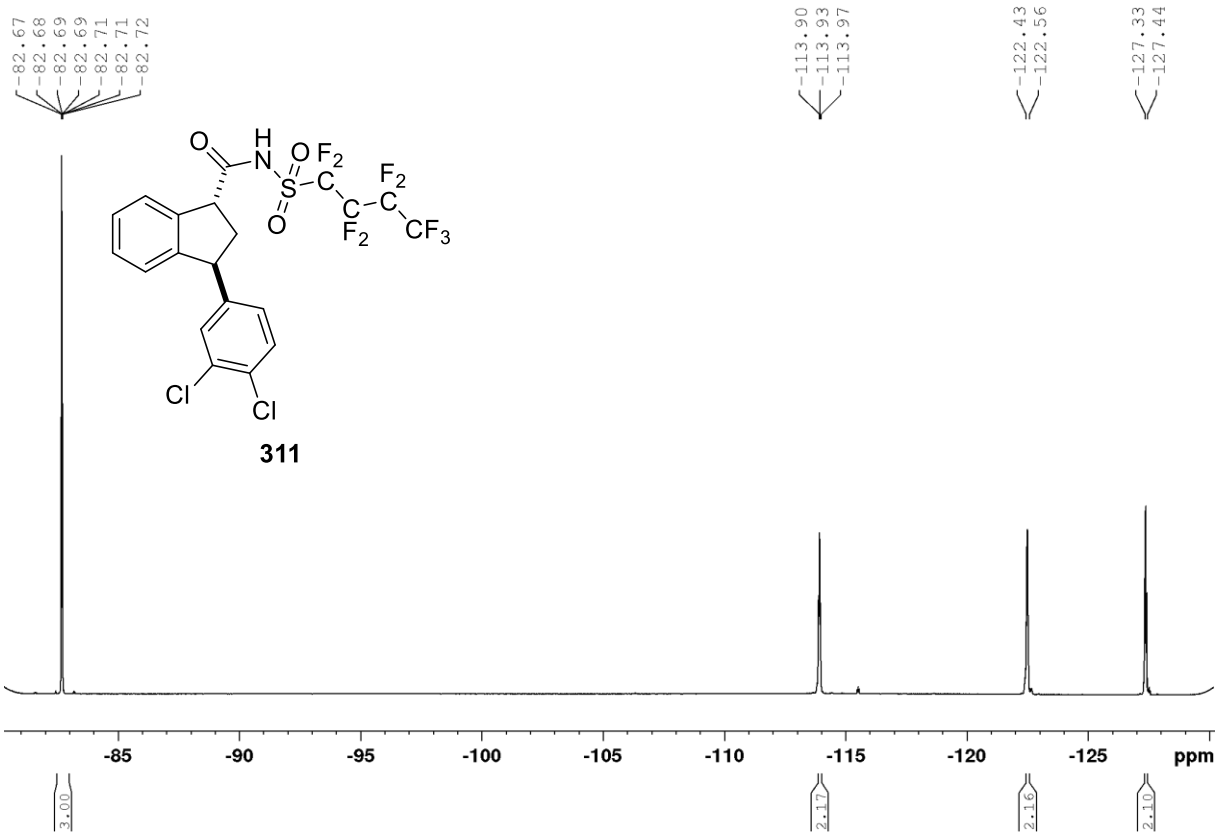


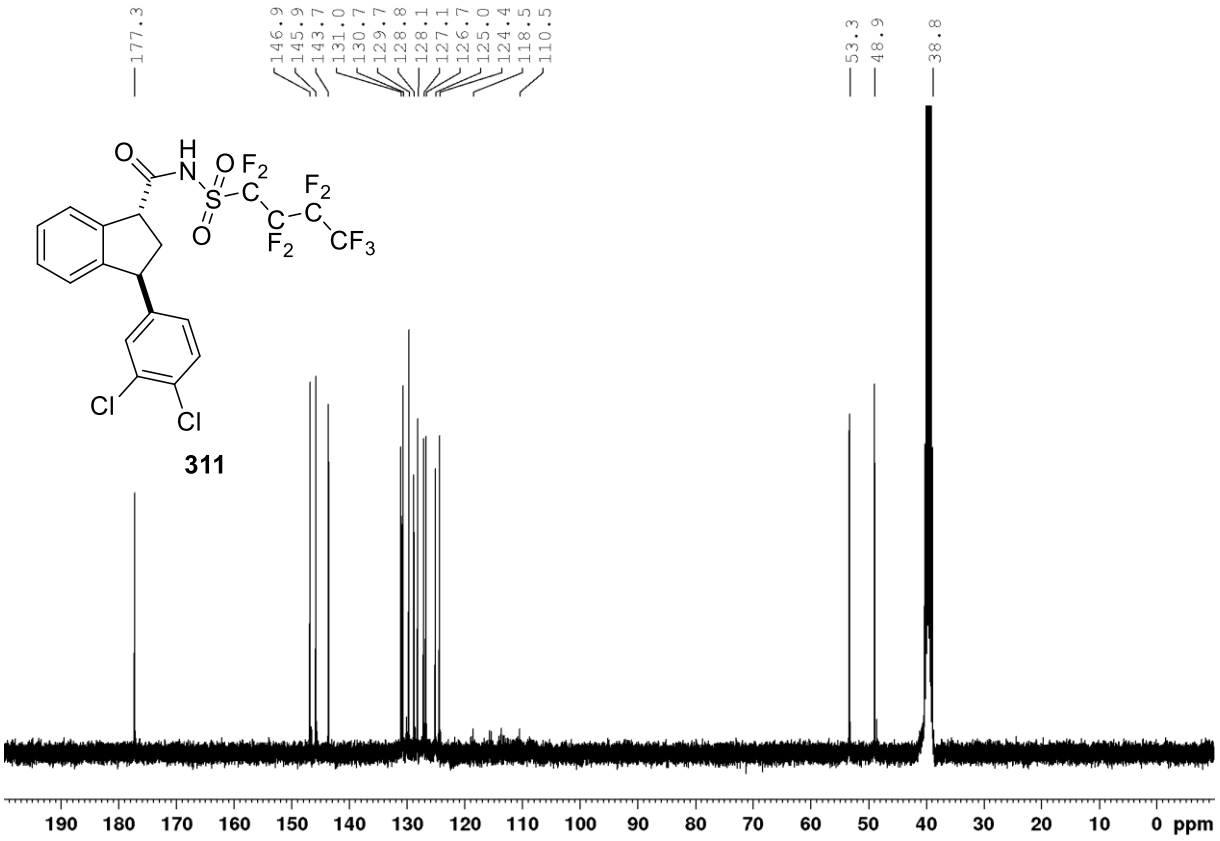
E40

(±)-(1*R*,3*S*)-3-(3,4-Dichlorophenyl)-*N*-((perfluorobutyl)sulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide (311)

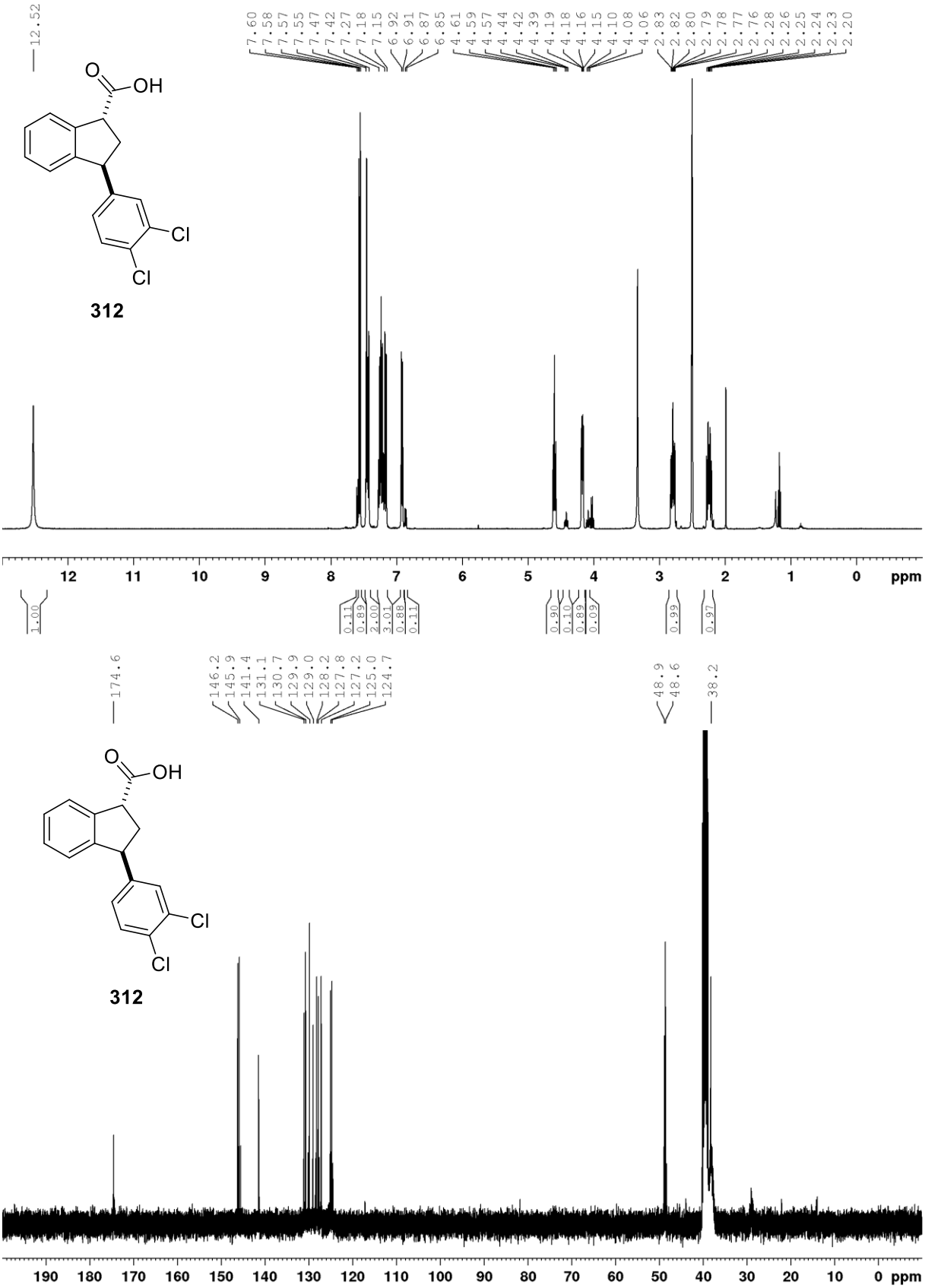


311

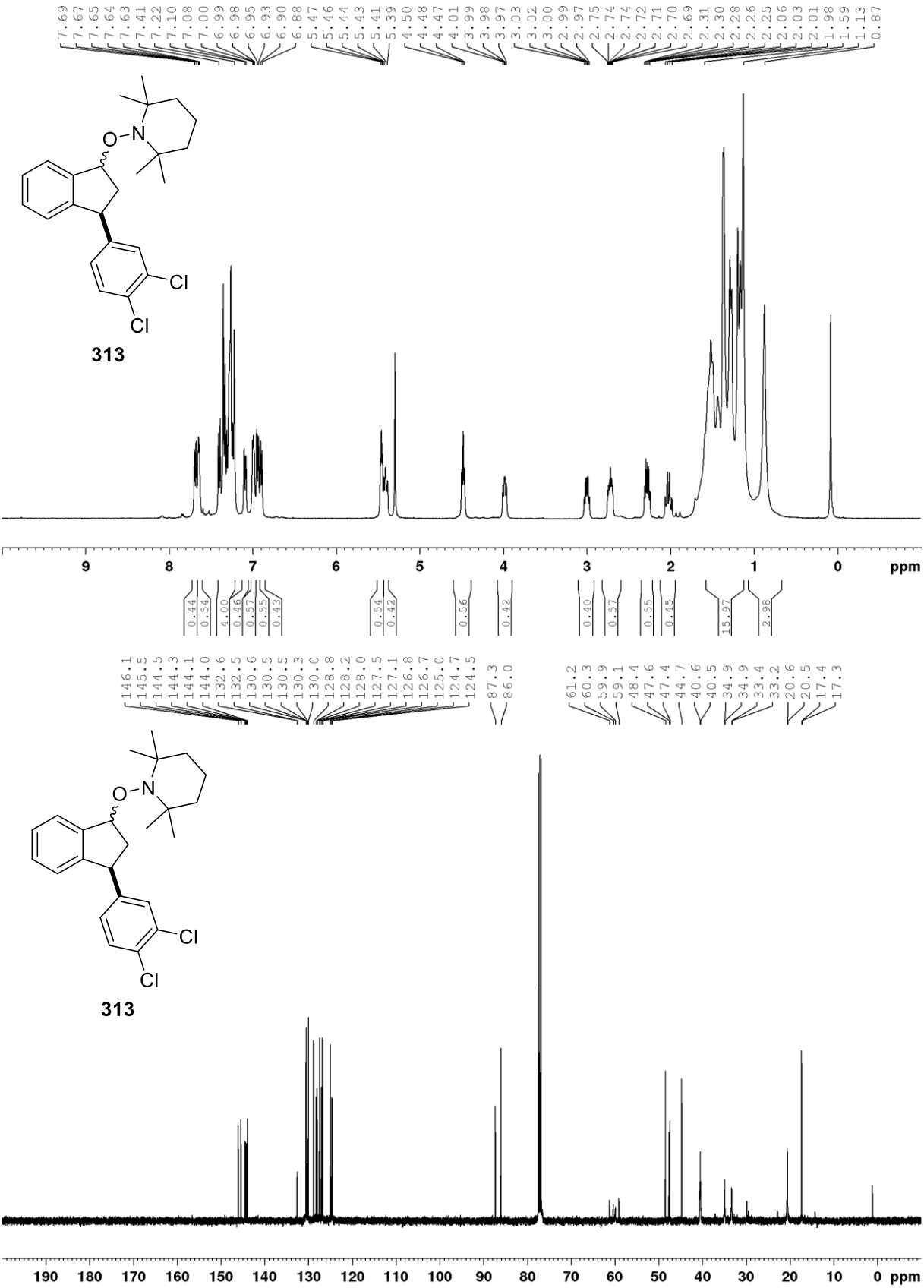

-82.67
-82.68
-82.69
-82.69
-82.71
-82.71
-82.72
-113.90
-113.93
-113.97
-122.43
-122.56
-127.33
-127.44
311
-85
-90
-95
-100
-105
-110
-115
-120
-125
ppm
3.00
2.17
2.16
2.10


177.3
146.9
145.9
143.7
131.0
130.7
129.7
128.8
128.1
127.1
126.7
125.0
124.4
118.5
110.5
53.3
48.9
38.8
311
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

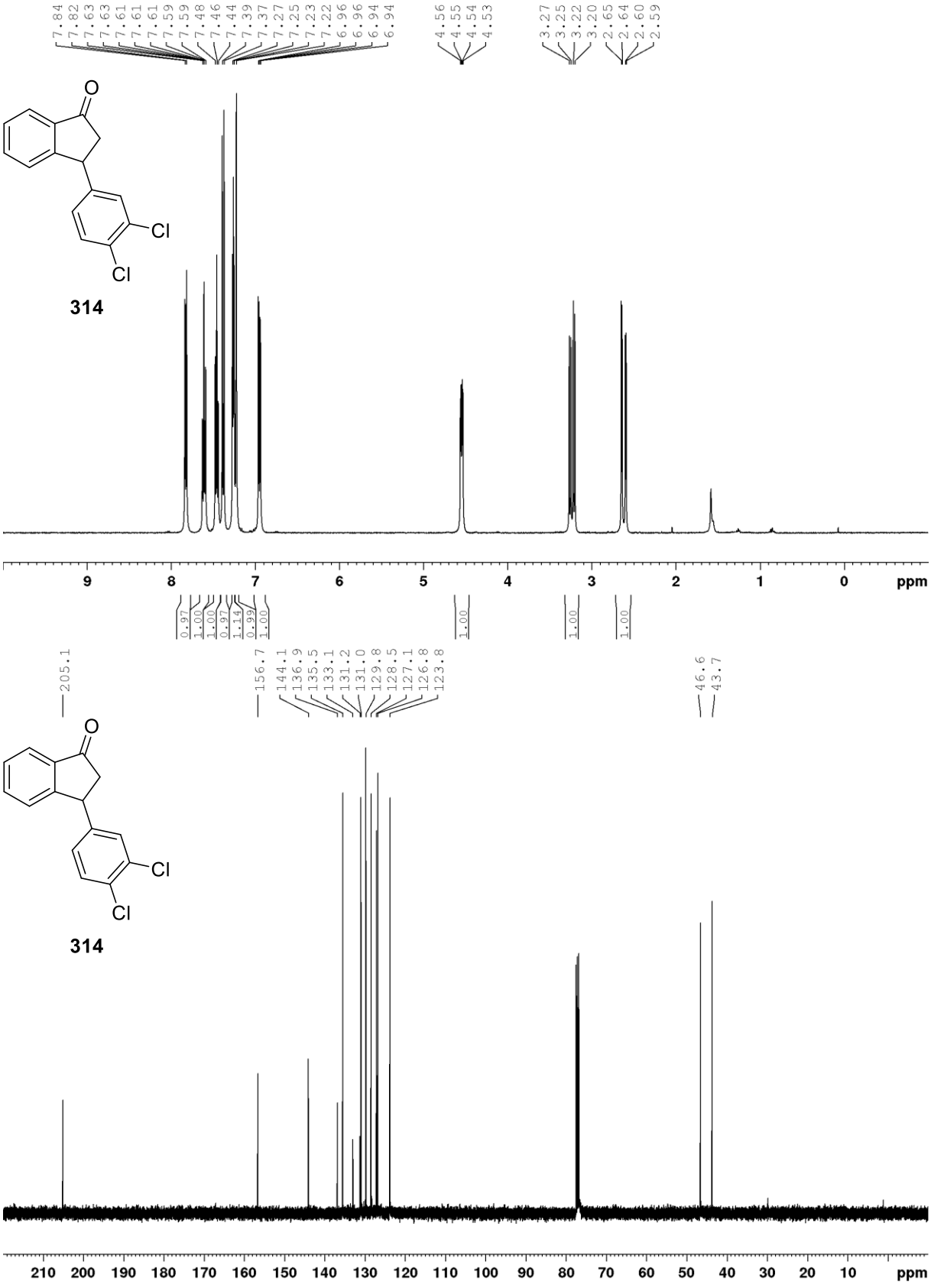
(±)-(1*R*,3*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid (312)



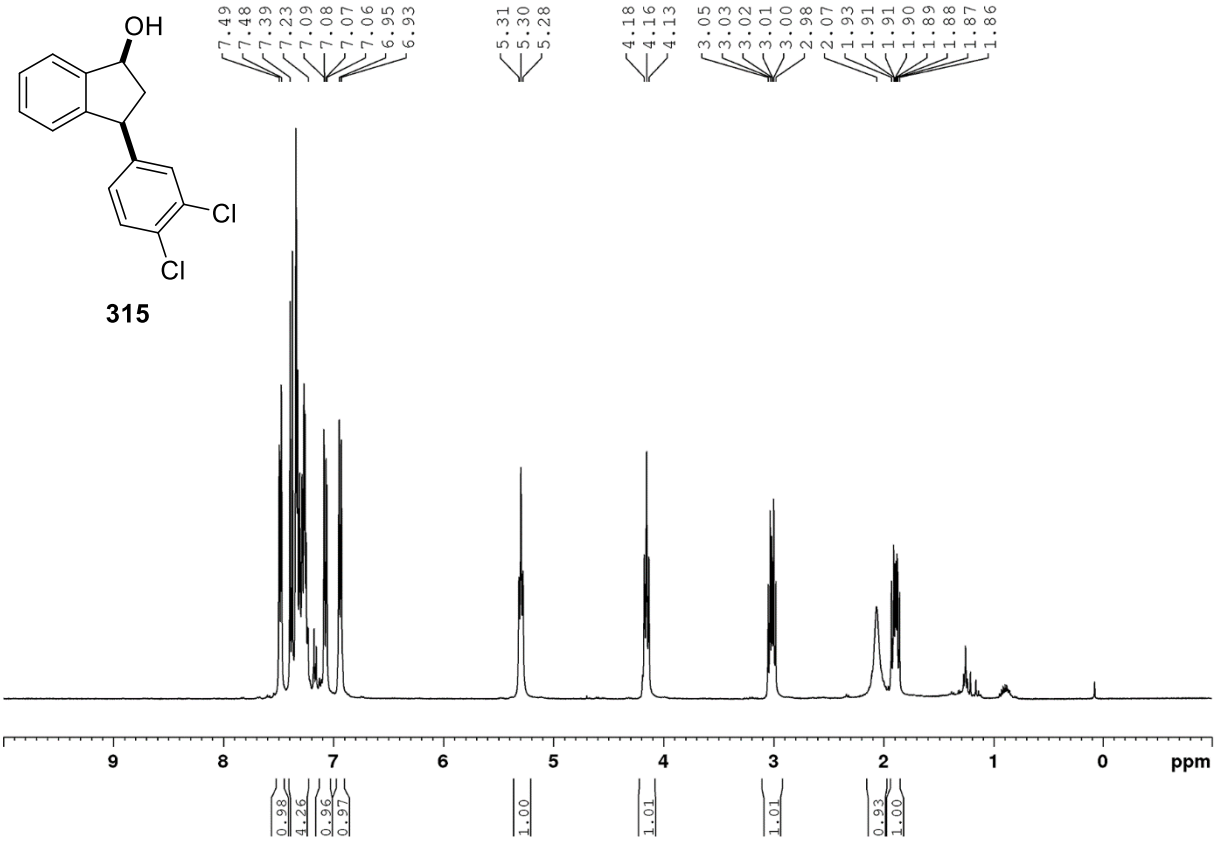
1-((3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (313)

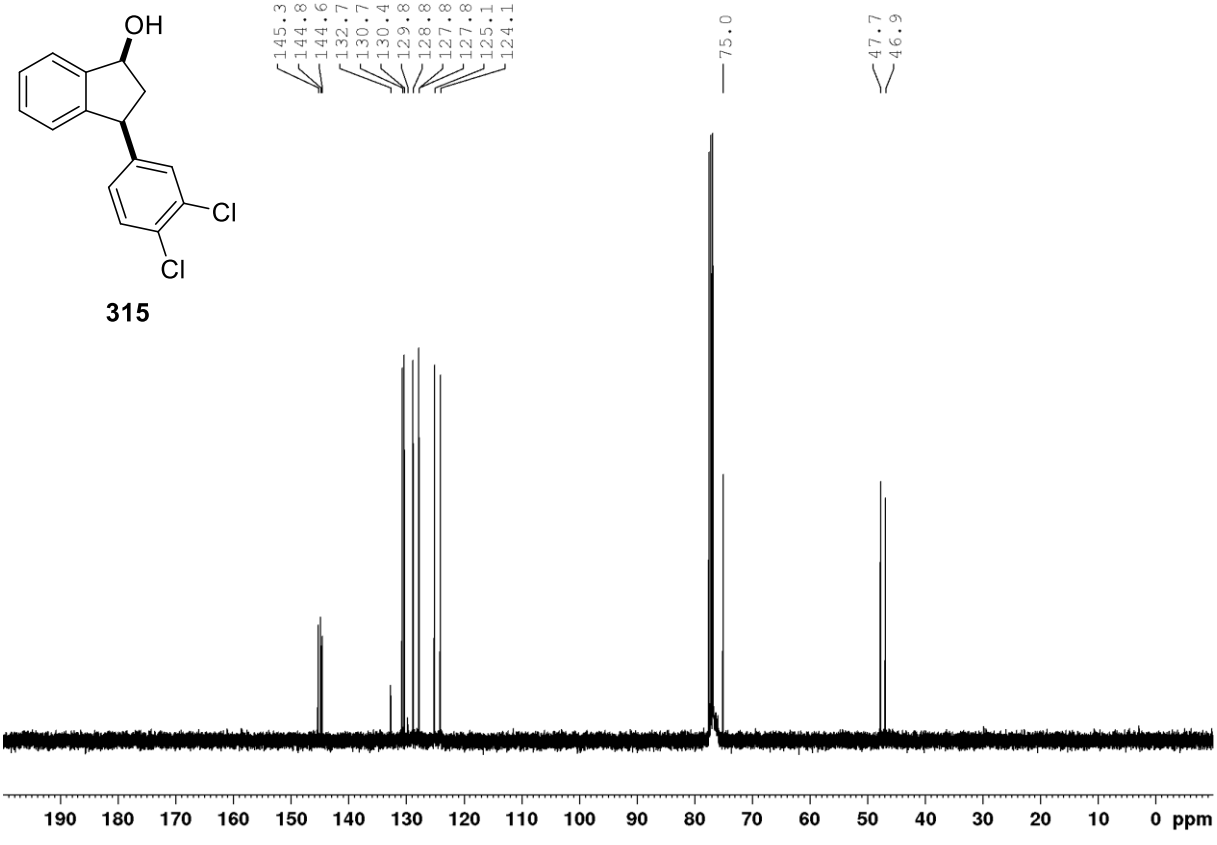


3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one (314)

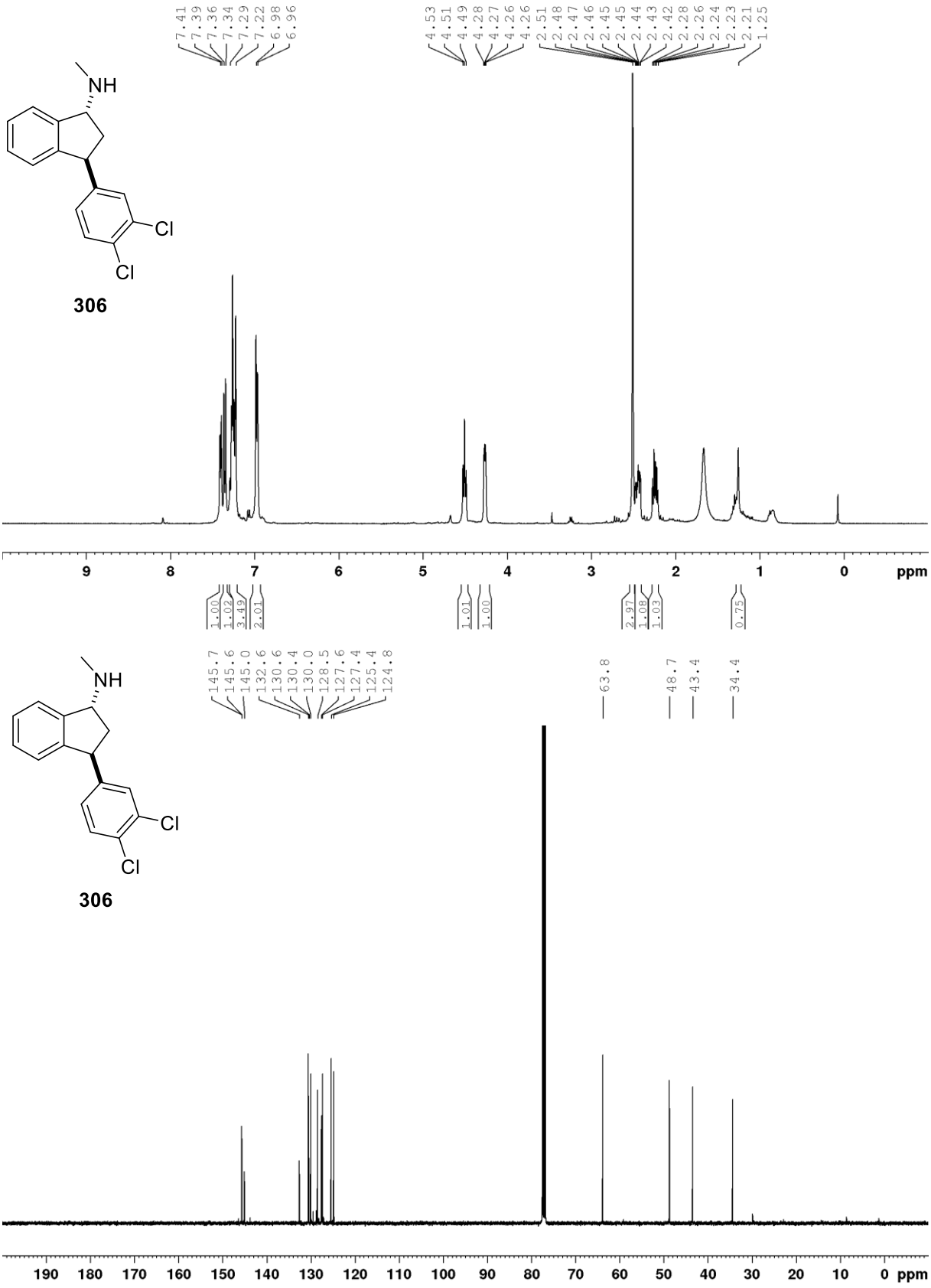


(±)-(1*S*,3*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (315)

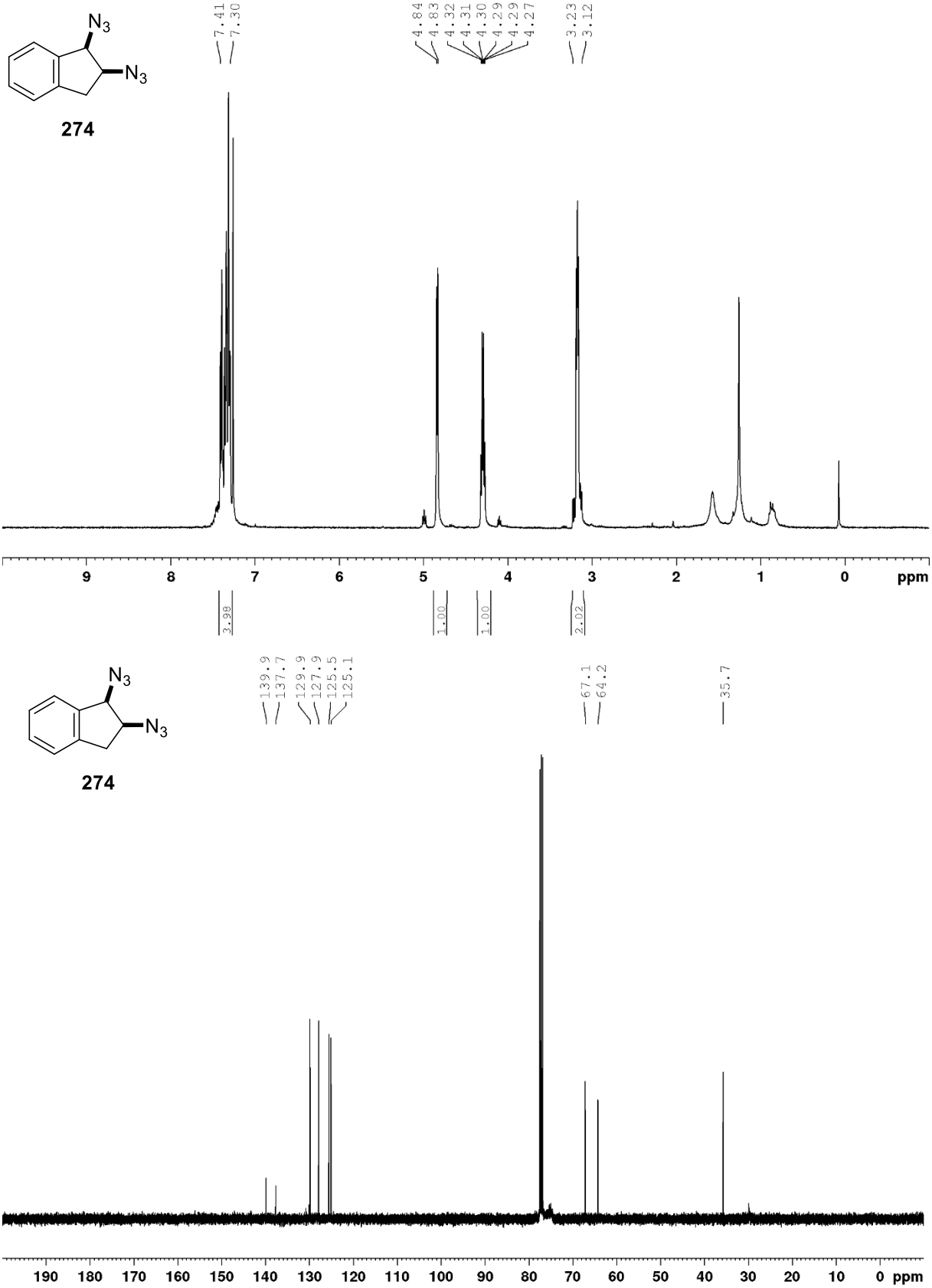


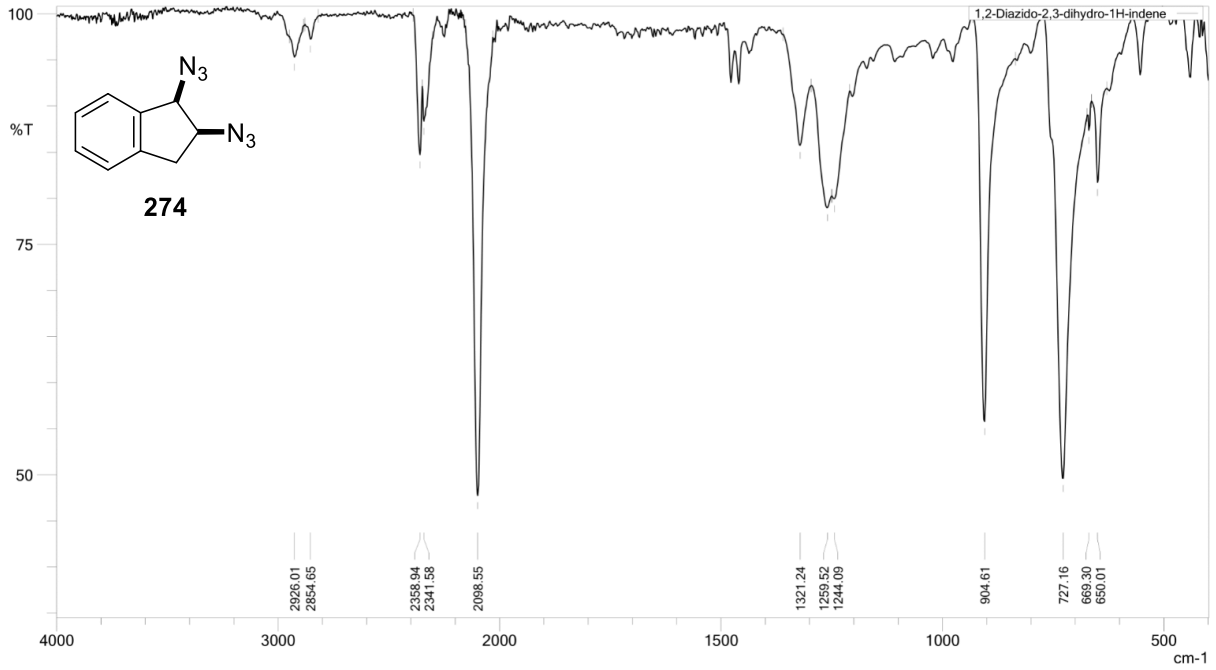


(±)-(1*R*,3*S*)-3-(3,4-Dichlorophenyl)-*N*-methyl-2,3-dihydro-1*H*-inden-1-amine ((±)-Indatraline, 305)

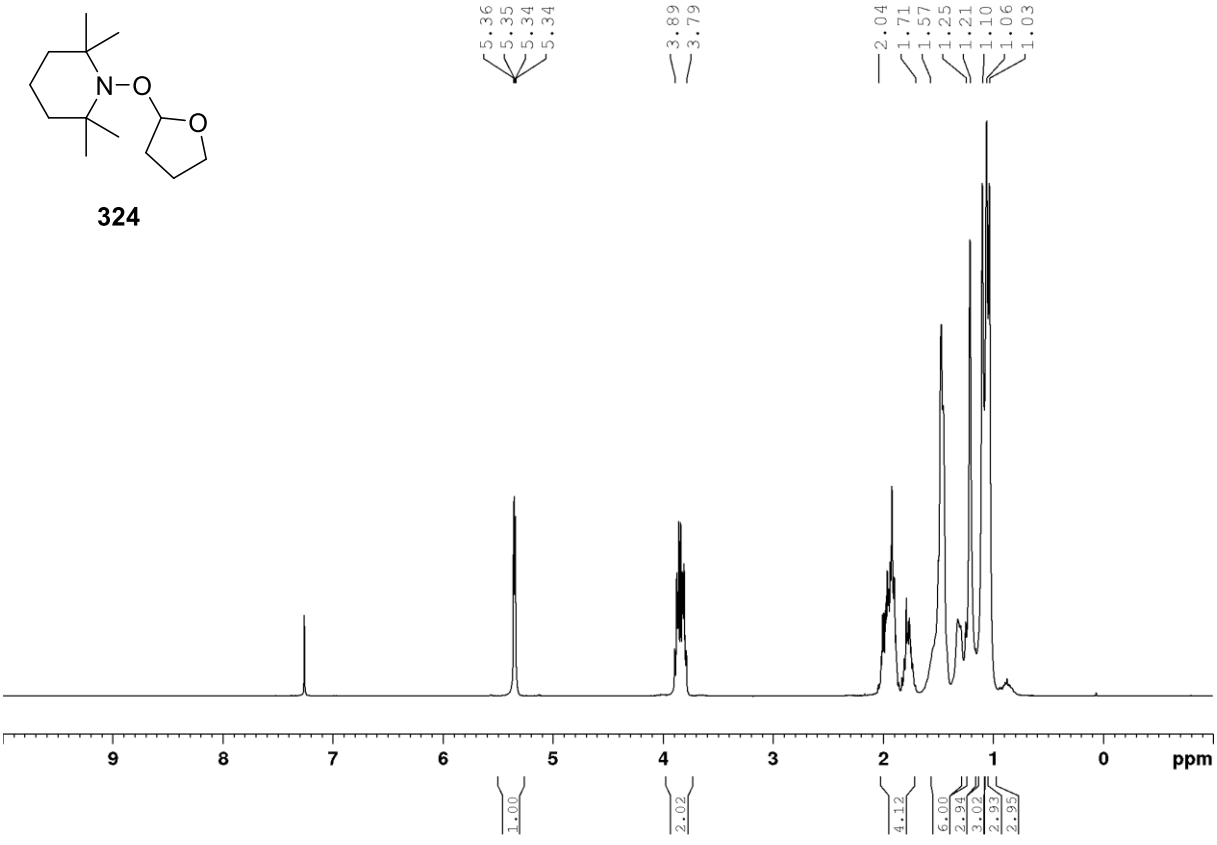


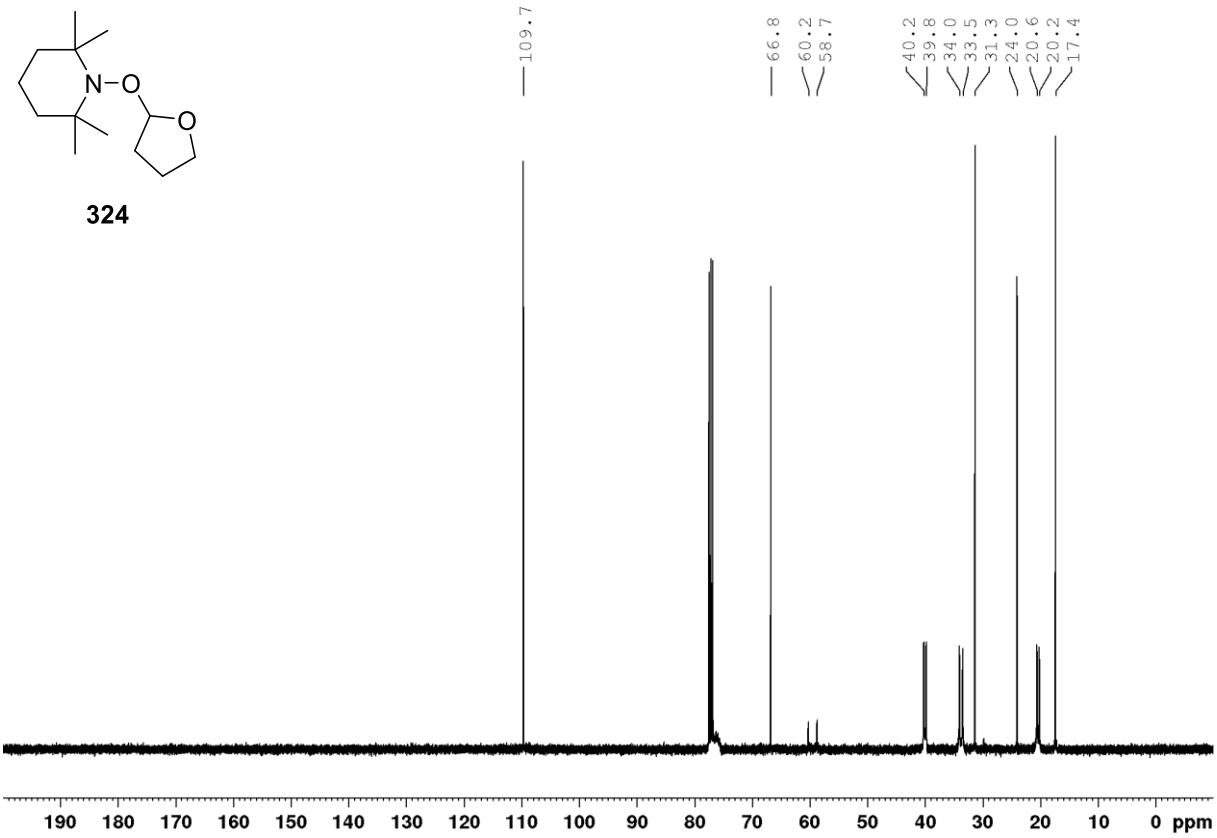
(±)-(1*R*,2*S*)-1,2-Diazido-2,3-dihydro-1*H*-indene (274)





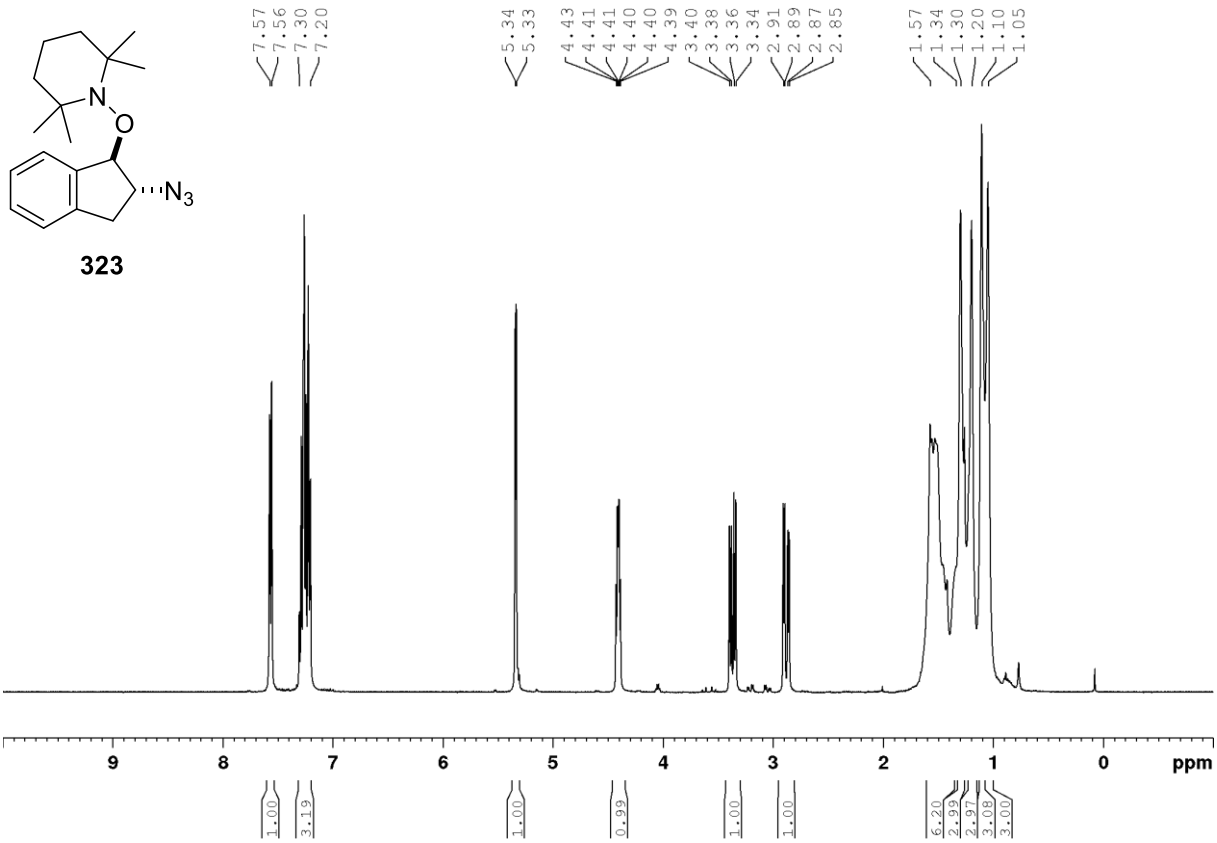
2,2,6,6-Tetramethyl-1-((tetrahydrofuran-2-yl)oxy)piperidine (324)



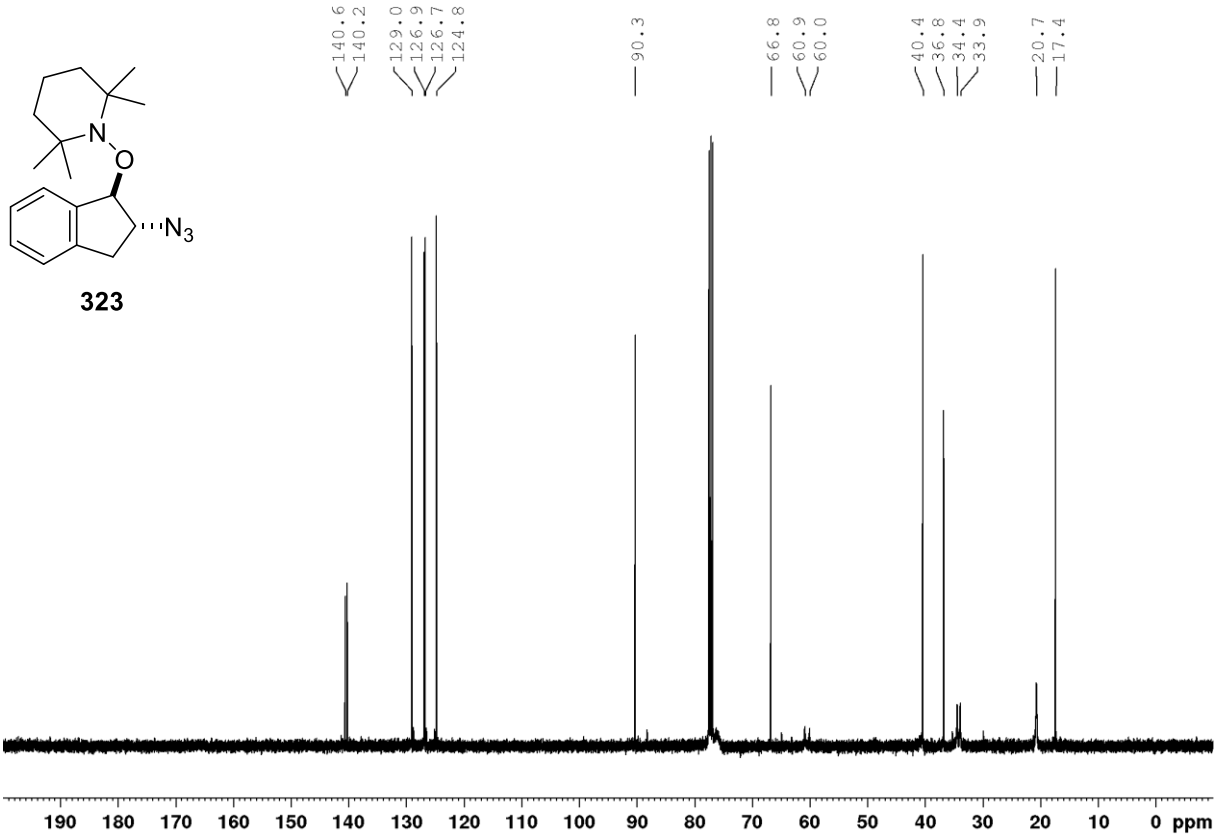


324

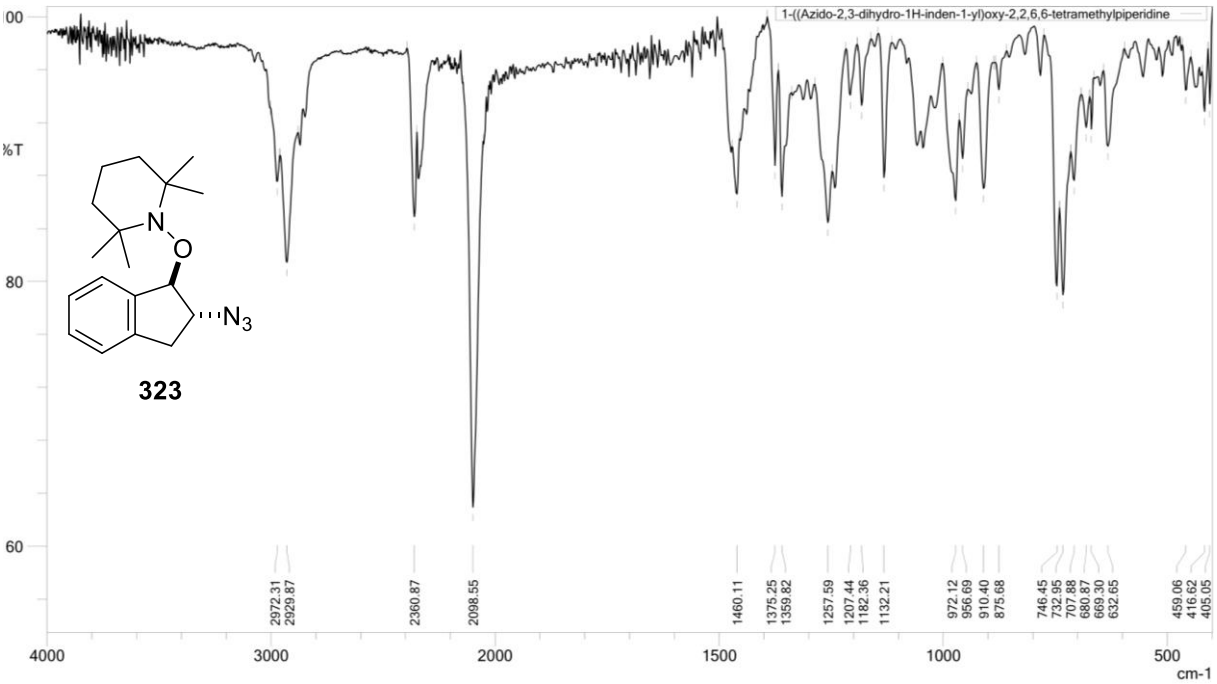
(±)-1-(((1*R*,2*R*)-2-Azido-2,3-dihydro-1*H*-inden-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (323)



323

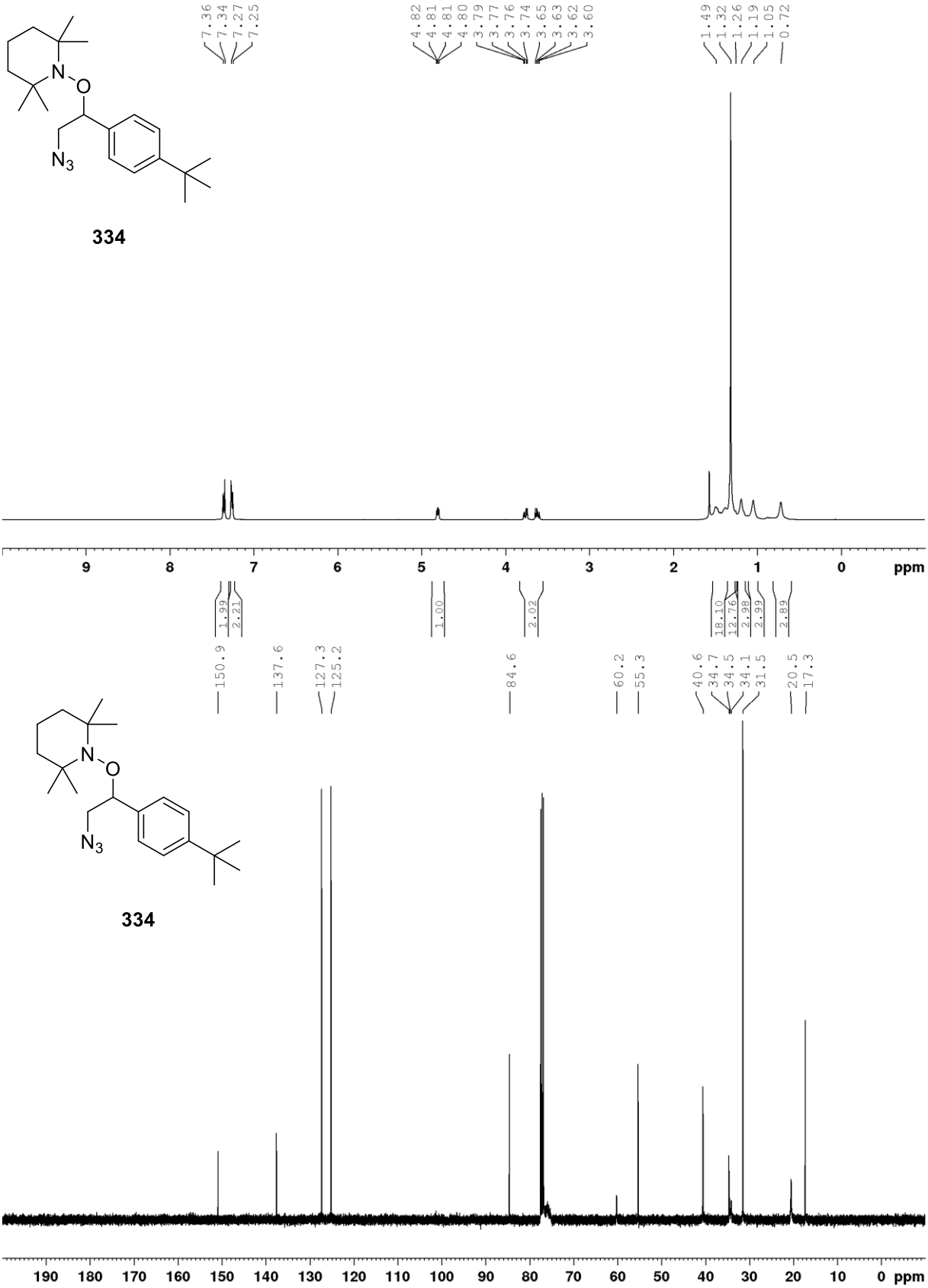

140.6
140.2
129.0
126.9
126.7
124.8
90.3
66.8
60.9
60.0
40.4
36.8
34.4
33.9
20.7
17.4
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

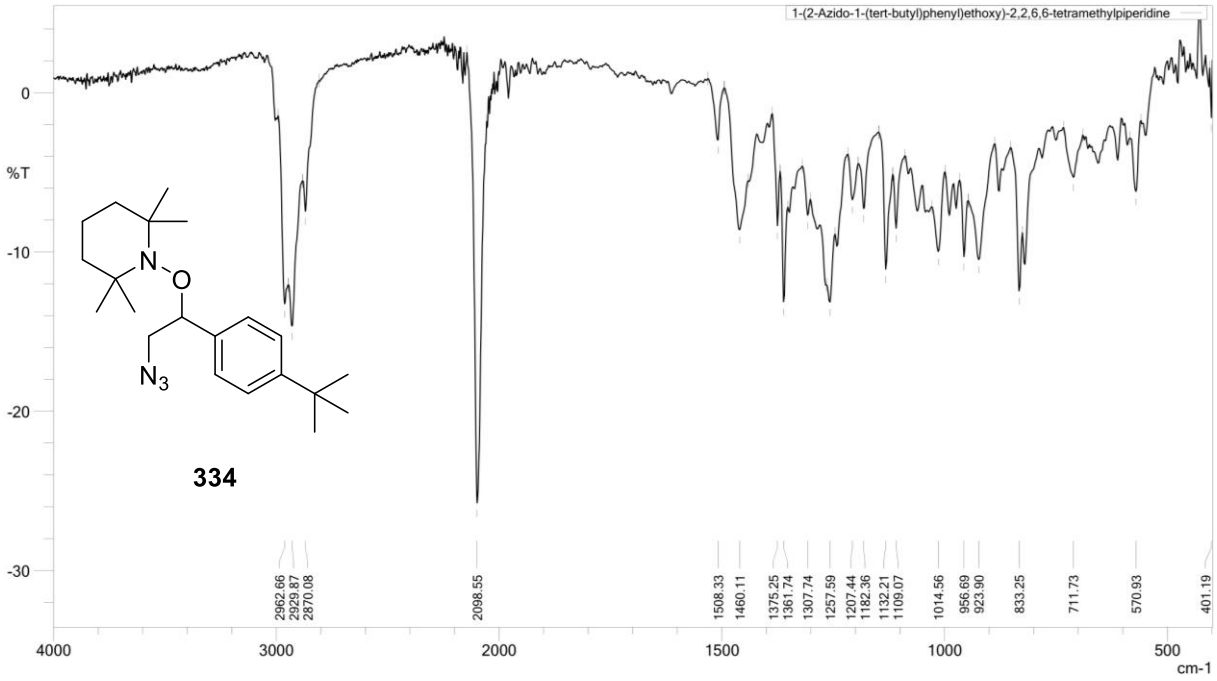
323


1-((Azido-2,3-dihydro-1H-inden-1-yl)oxy-2,2,6,6-tetramethylpiperidine
%T
2972.31
2929.87
2360.87
2098.55
1460.11
1375.25
1359.82
1257.59
1207.44
1182.36
1132.21
972.12
956.69
910.40
875.68
746.45
732.95
707.88
680.87
669.30
632.65
459.06
416.62
405.05
4000 3000 2000 1500 1000 500
cm-1

323

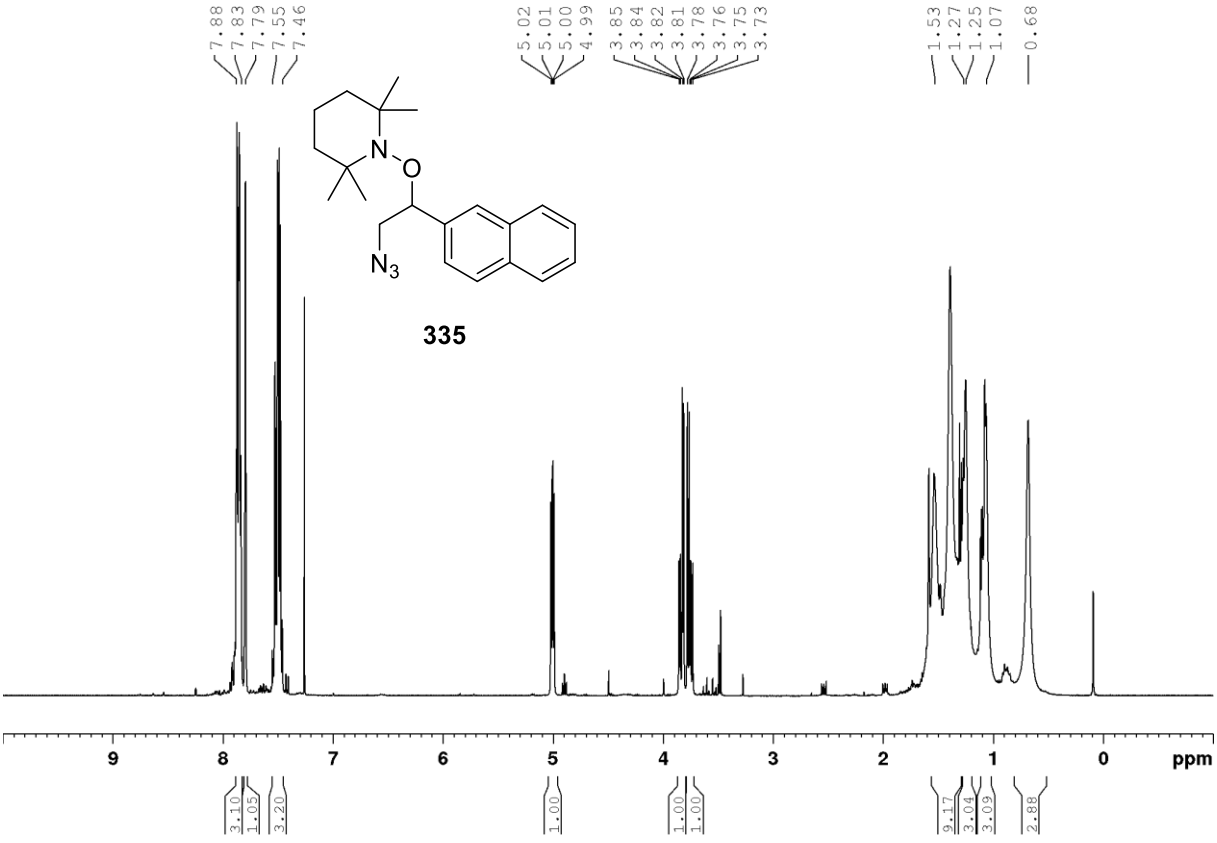
1-(2-Azido-1-(4-(*tert*-butyl)phenyl)ethoxy)-2,2,6,6-tetramethylpiperidine (334)



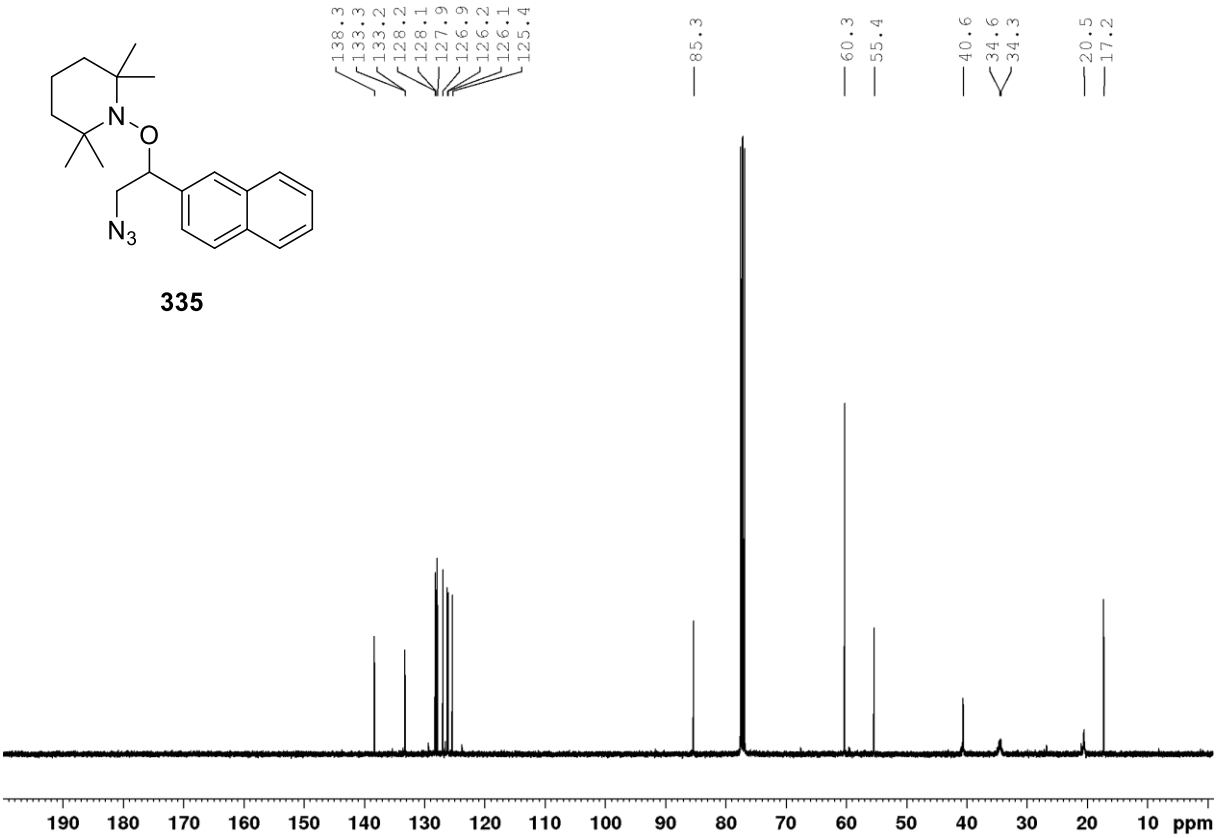


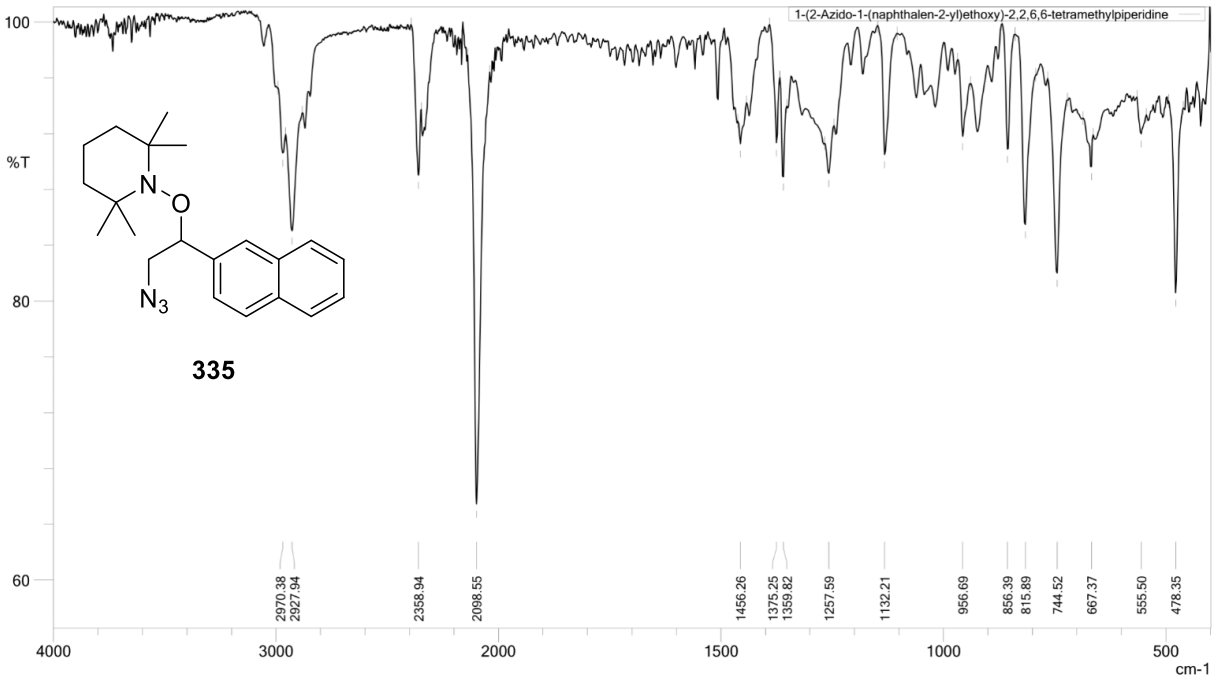
334

1-(2-Azido-1-(naphthalen-2-yl)ethoxy)-2,2,6,6-tetramethylpiperidine (335)

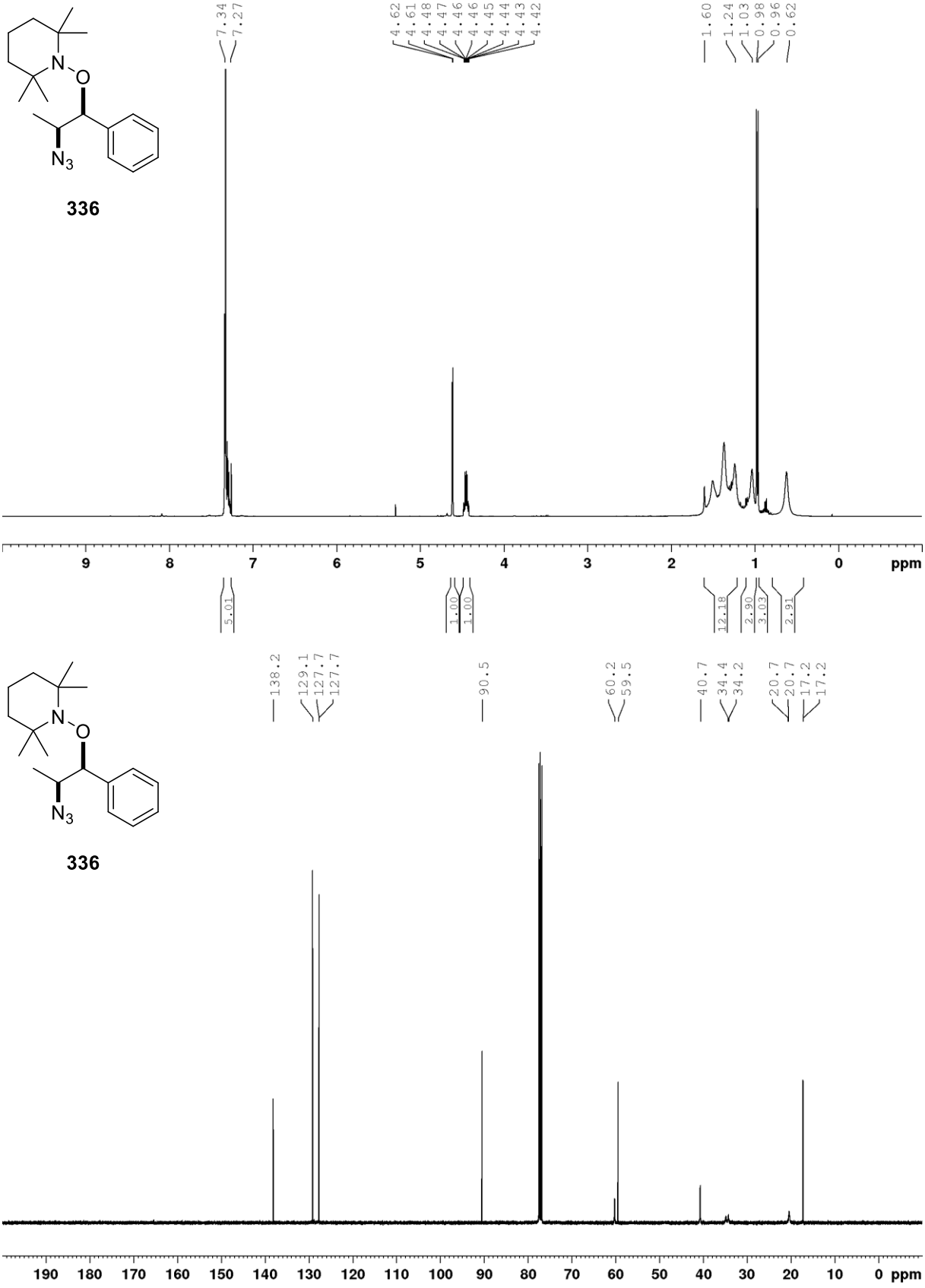


335

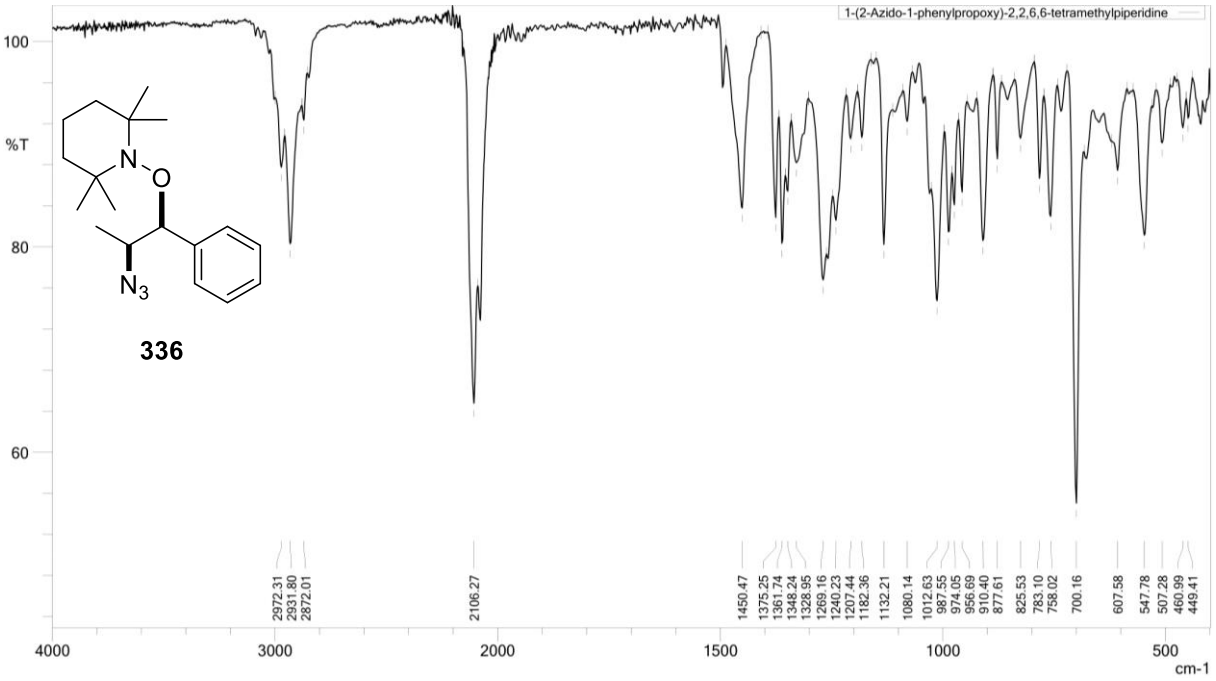

138.3
133.3
133.2
128.2
128.1
127.9
126.9
126.2
126.1
125.4
85.3
60.3
55.4
40.6
34.6
34.3
20.5
17.2
N
O
N3
335
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1-(2-Azido-1-(naphthalen-2-yl)ethoxy)-2,2,6,6-tetramethylpiperidine
100
%T
80
60
N
O
N3
335
2970.38
2927.94
2358.94
2098.55
1456.26
1375.25
1359.82
1257.59
1132.21
956.69
856.39
815.89
744.52
667.37
555.50
478.35
4000
3000
2000
1500
1000
500
cm-1

(±)-1-((1*S*,2*S*)-2-Azido-1-phenylpropoxy)-2,2,6,6-tetramethylpiperidine (336)



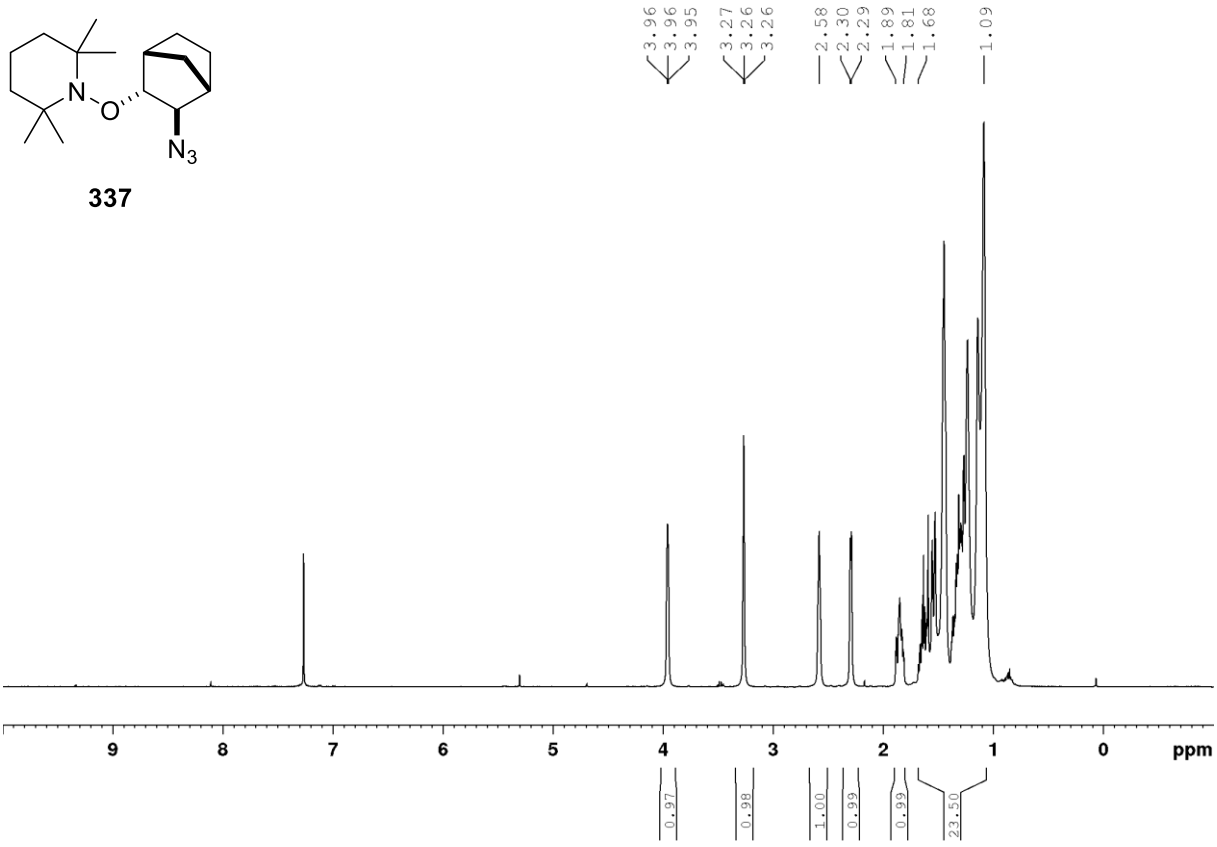
336

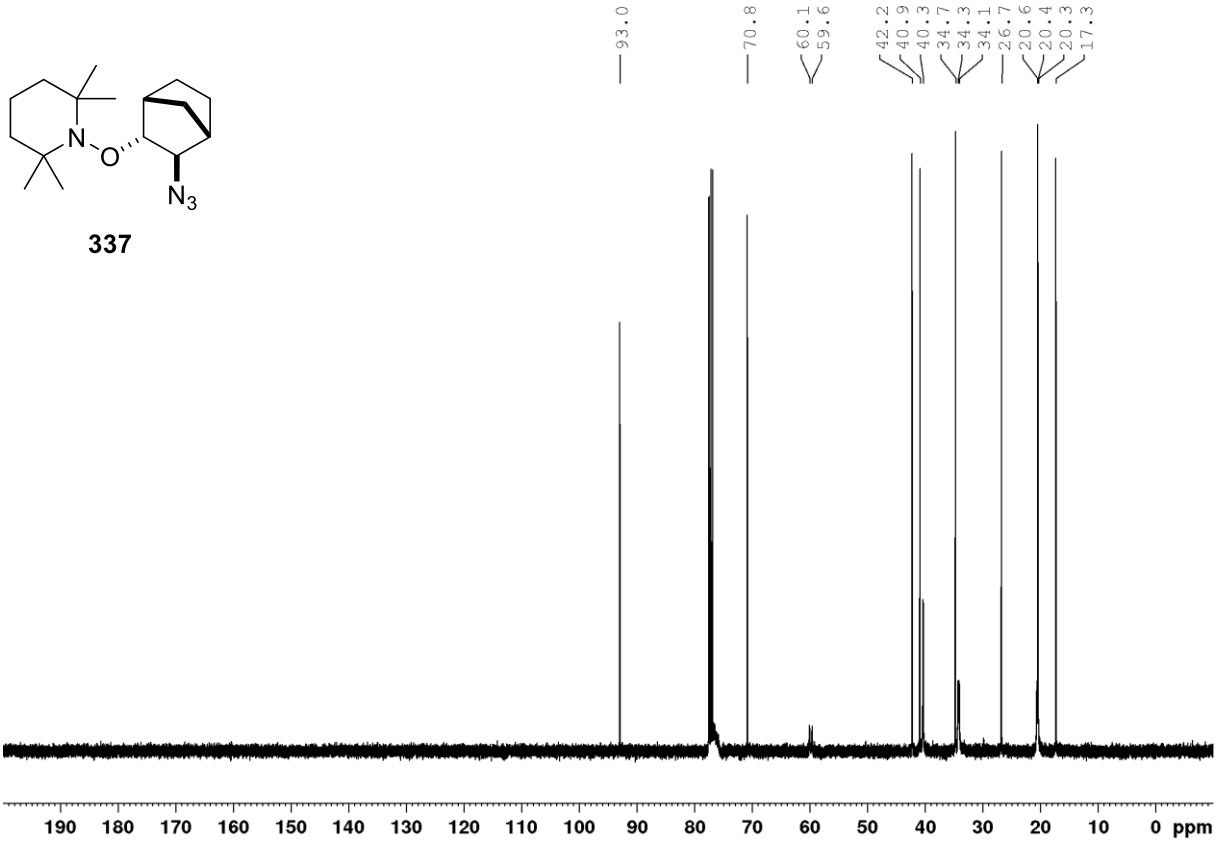


336

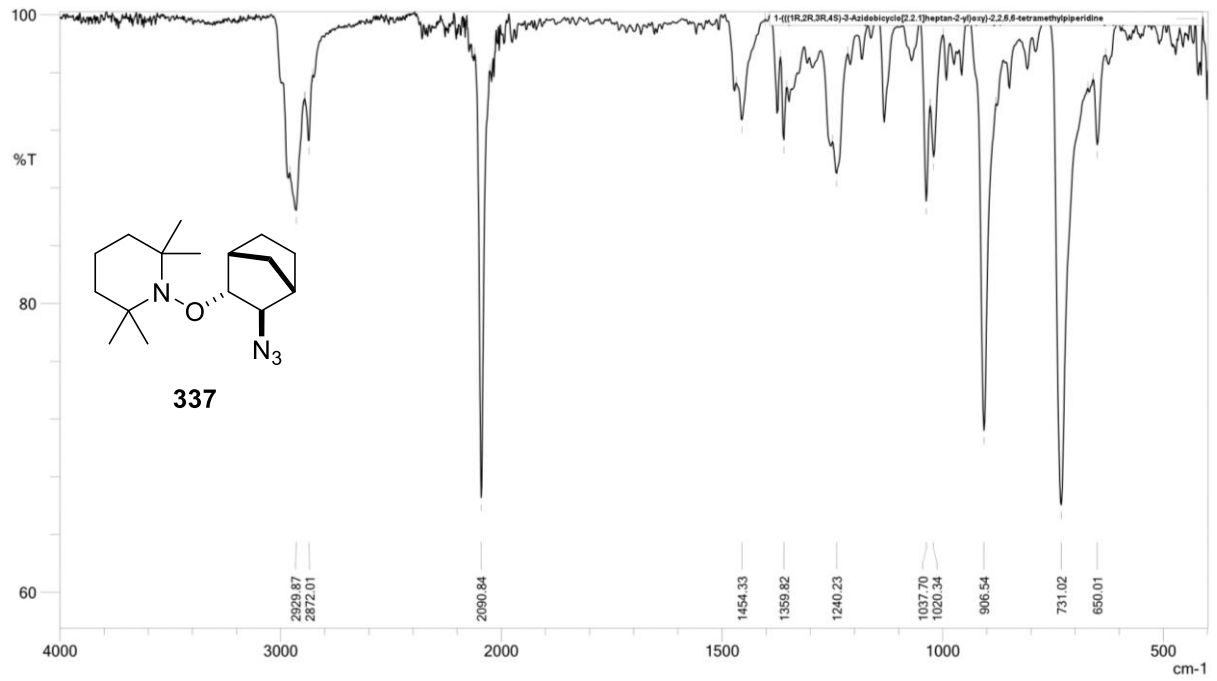
(±)-1-(((1*R*,2*R*,3*R*,4*S*)-3-Azidobicyclo[2.2.1]heptan-2-yl)oxy)-2,2,6,6-tetramethylpiperidine (337)

337



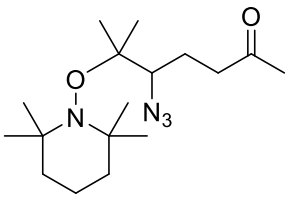

93.0
70.8
60.1
59.6
42.2
40.9
40.3
34.7
34.3
34.1
26.7
20.6
20.4
20.3
17.3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

337

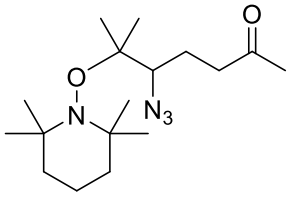

100
%T
80
60
2929.87
2872.01
2090.84
1454.33
1359.82
1240.23
1037.70
1020.34
906.54
731.02
650.01
4000
3000
2000
1500
1000
500
cm-1

337

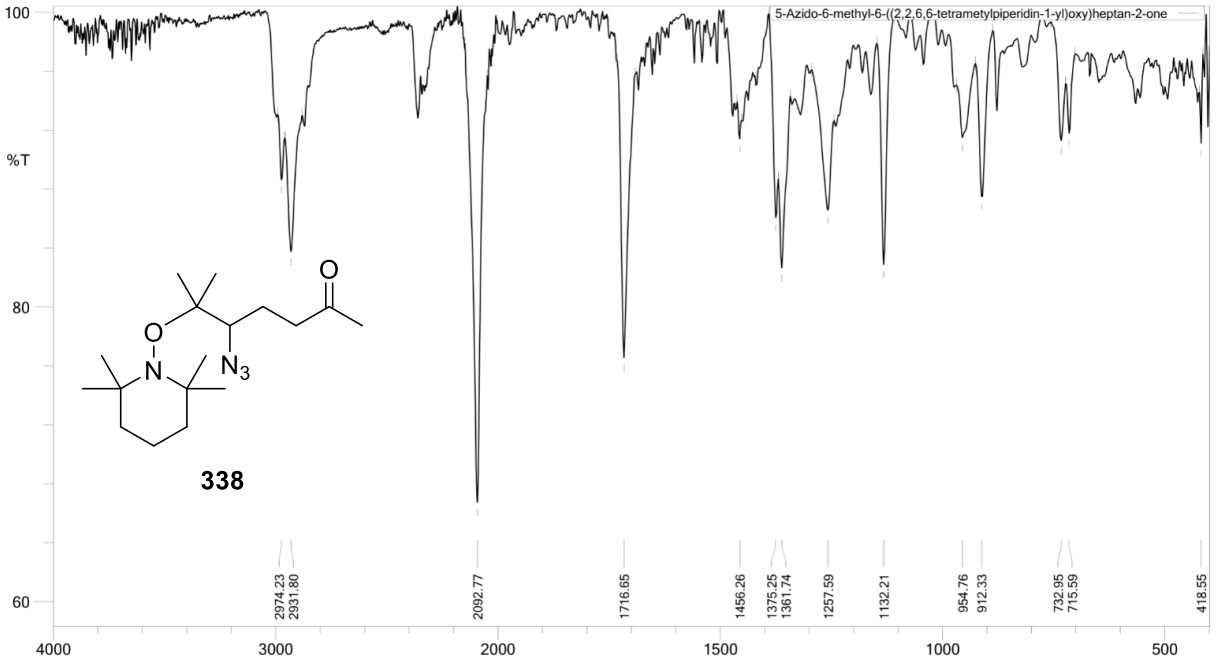
5-Azido-6-methyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)heptan-2-one (338)



338

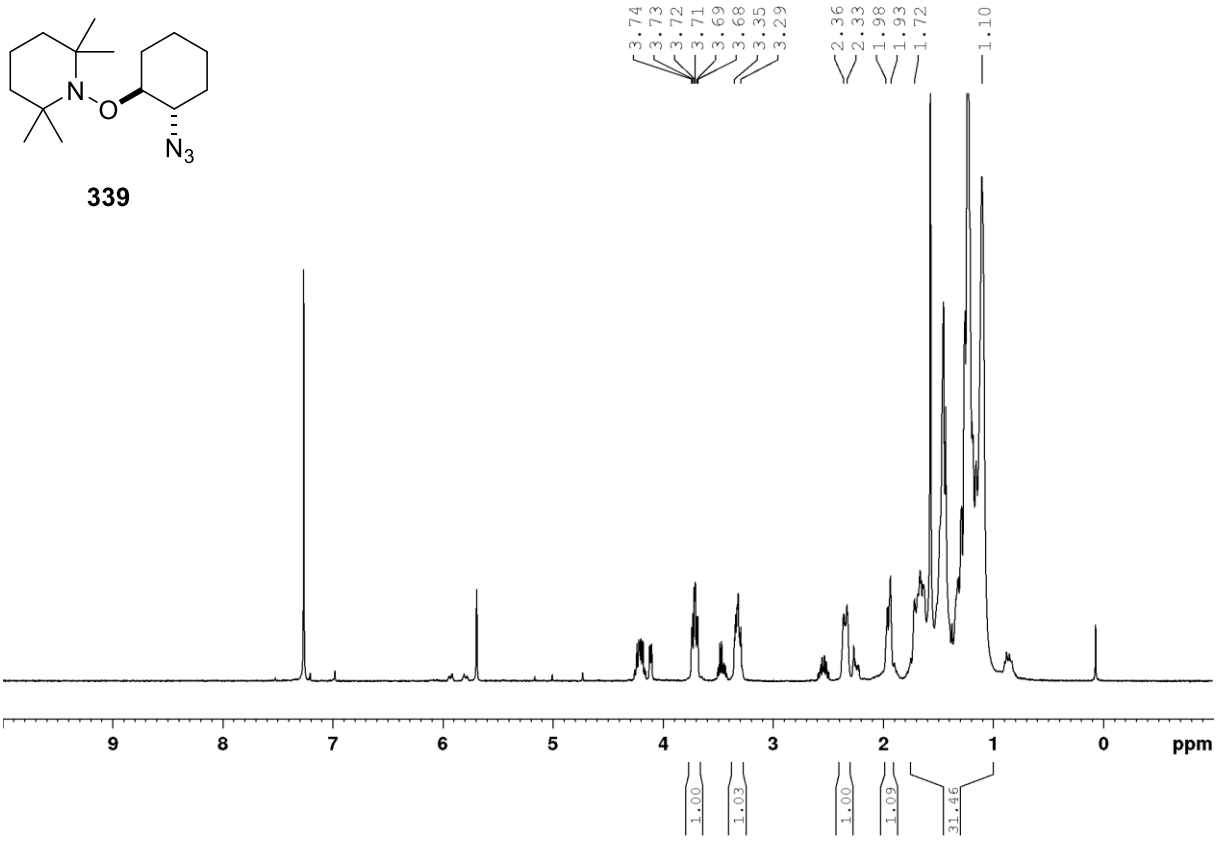


338

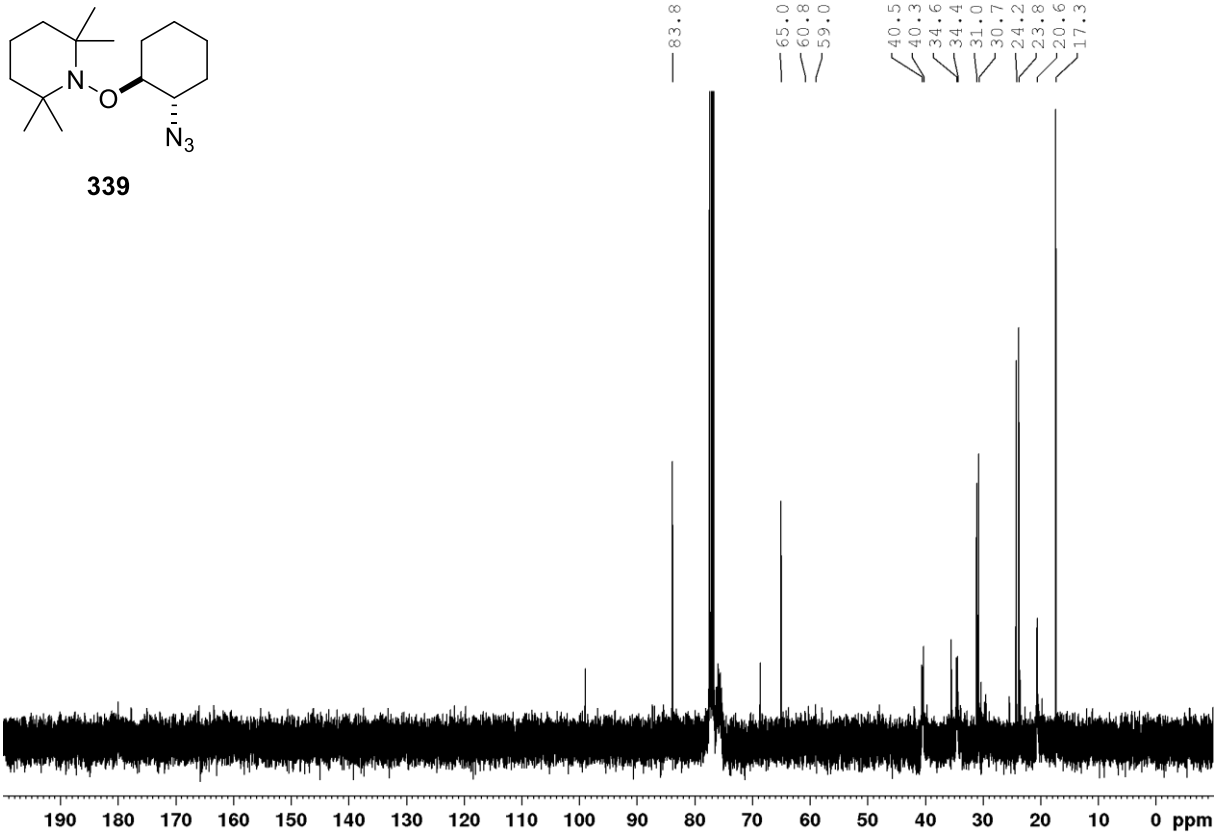


338

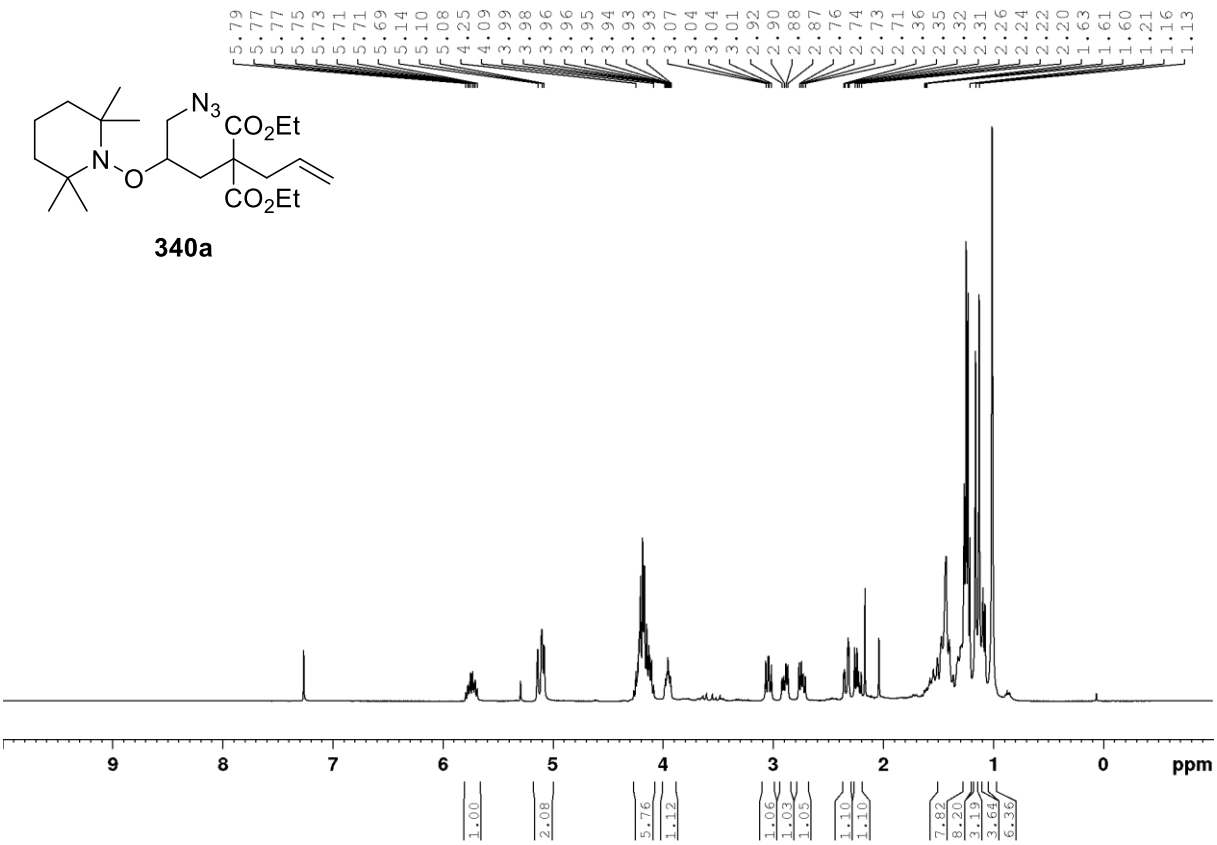
(±)-1-(((1*S*,2*S*)-2-Azidocyclohexyl)oxy)-2,2,6,6-tetramethylpiperidine (339)

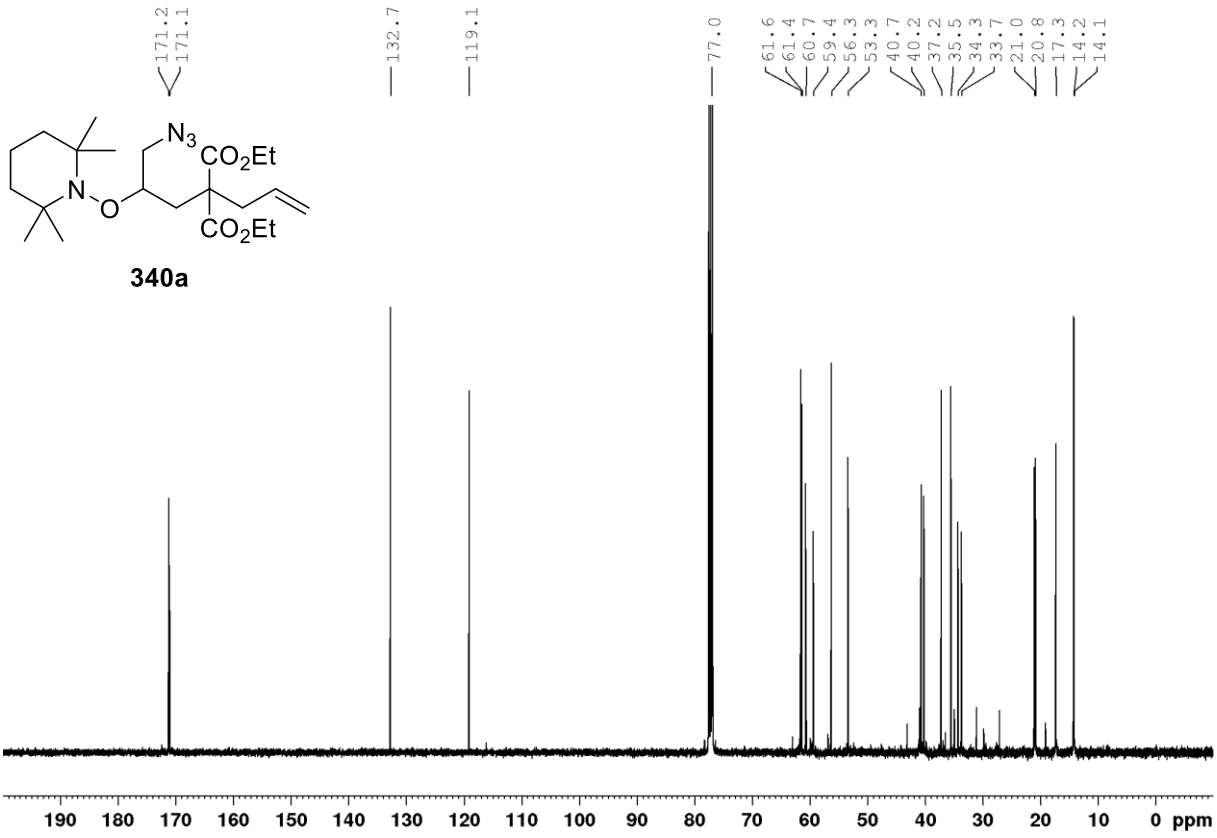


339



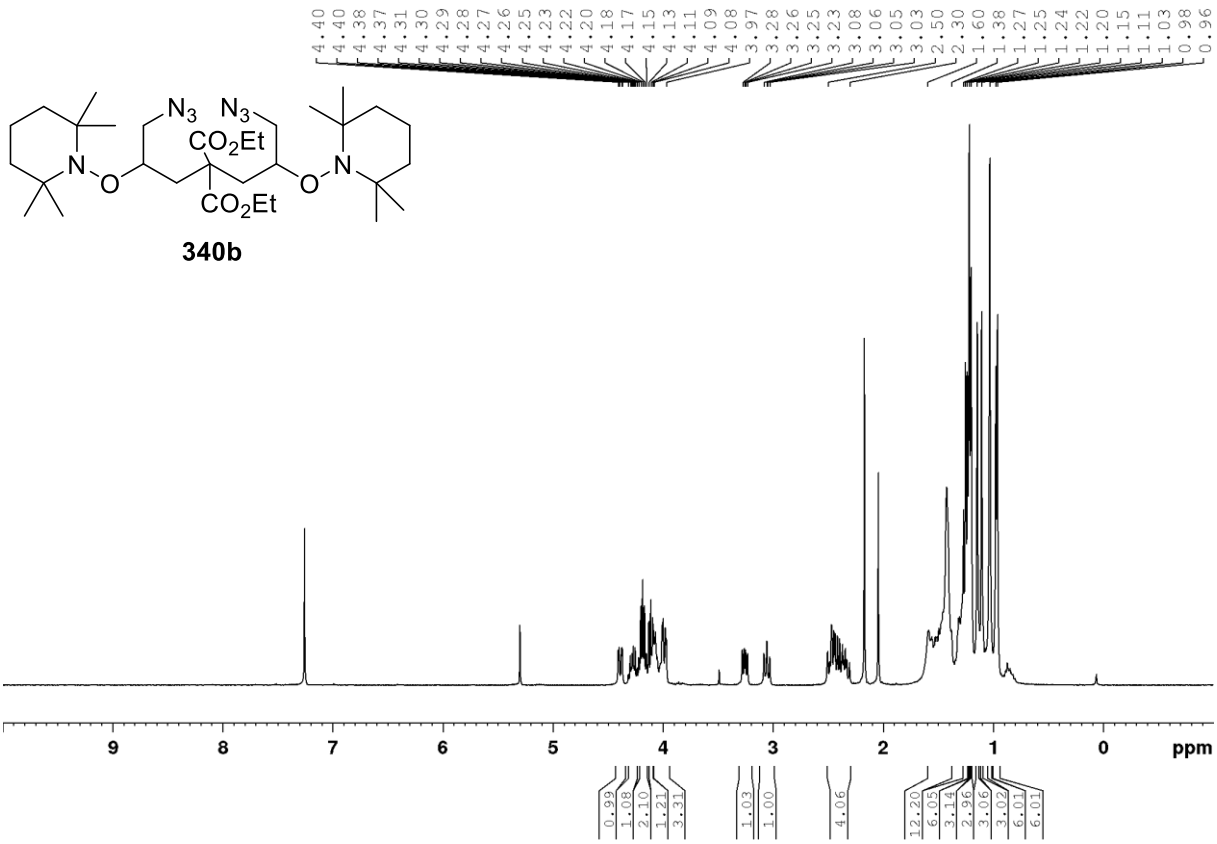
Diethyl 2-allyl-2-(3-azido-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)malonate (340a)



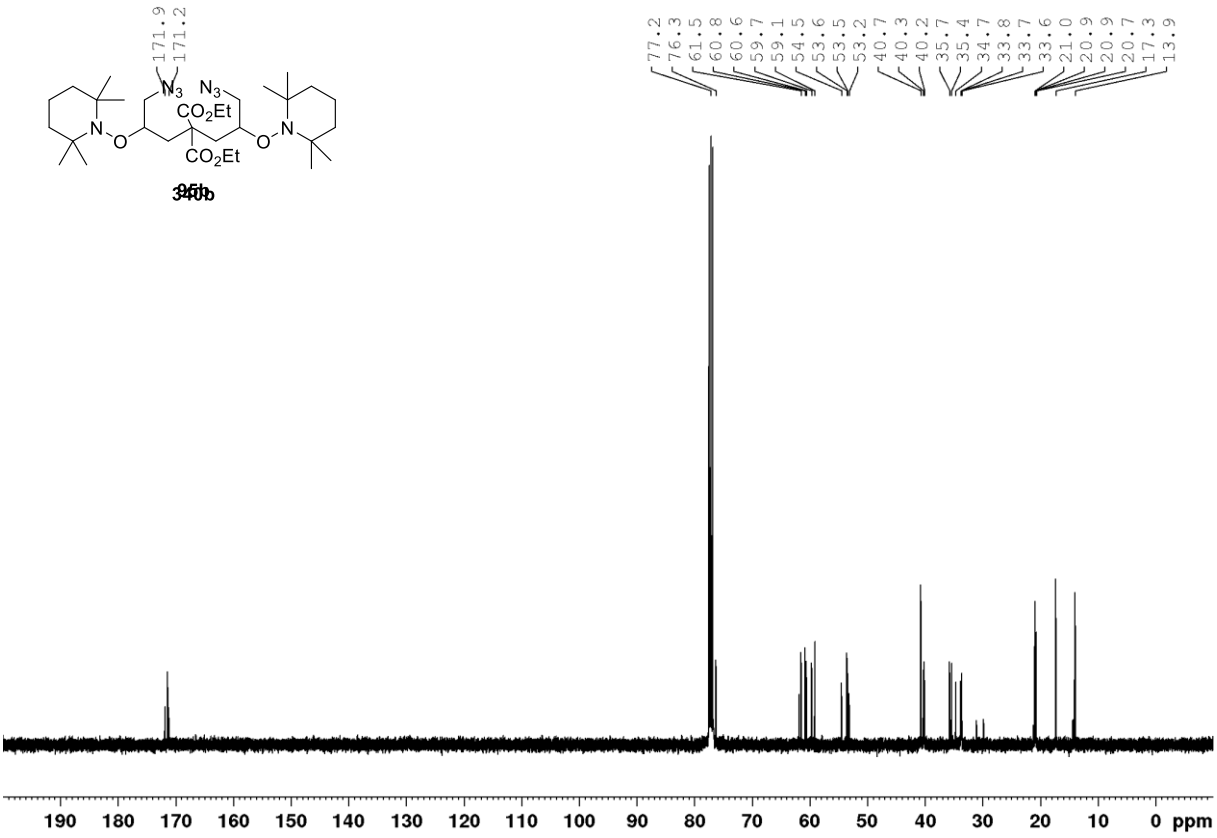


340a

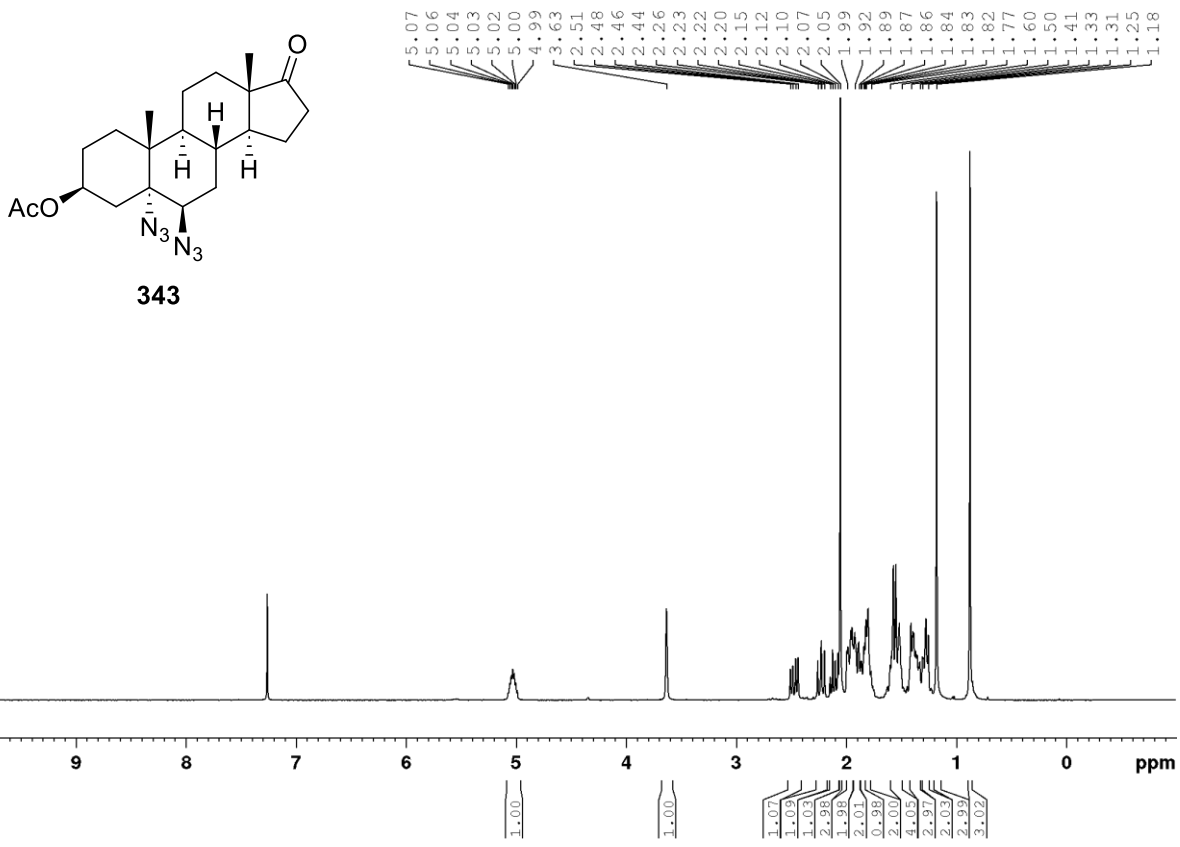
Diethyl 2,2-bis(3-azido-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)malonate (95b)



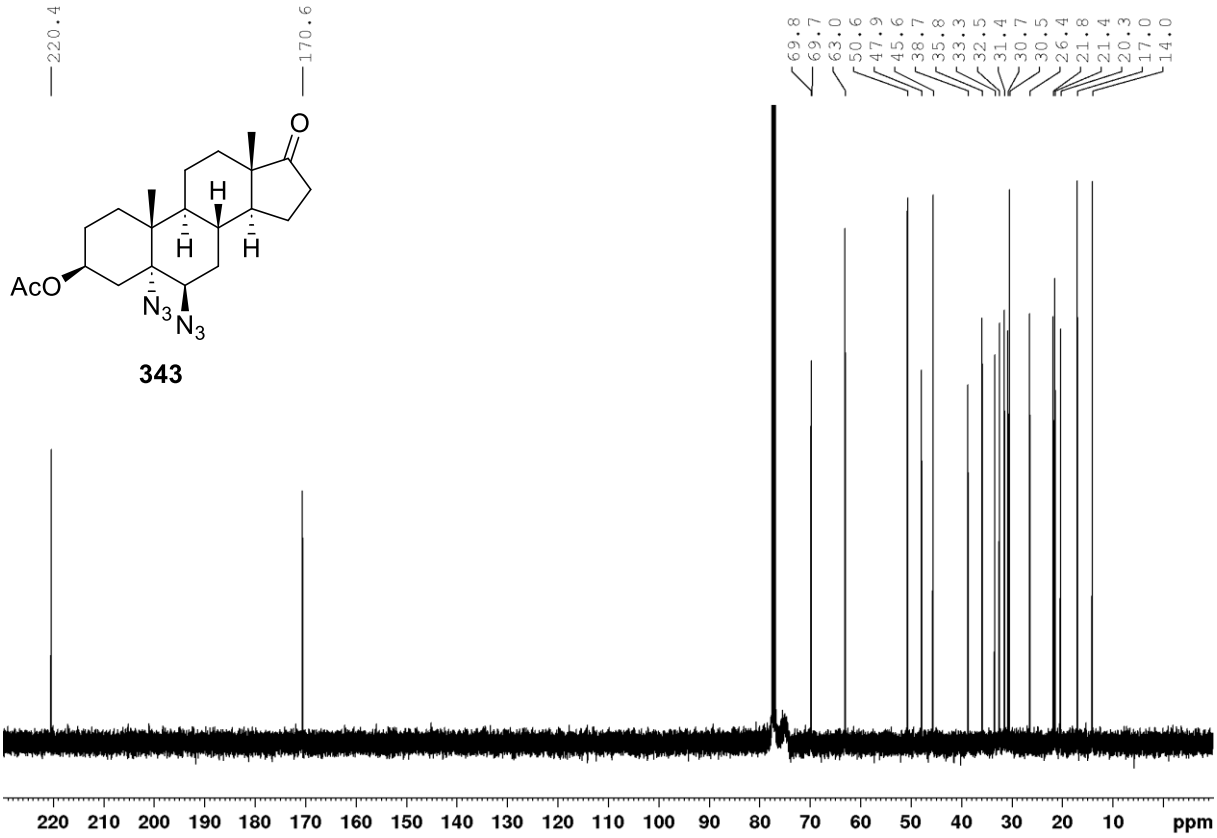
340b

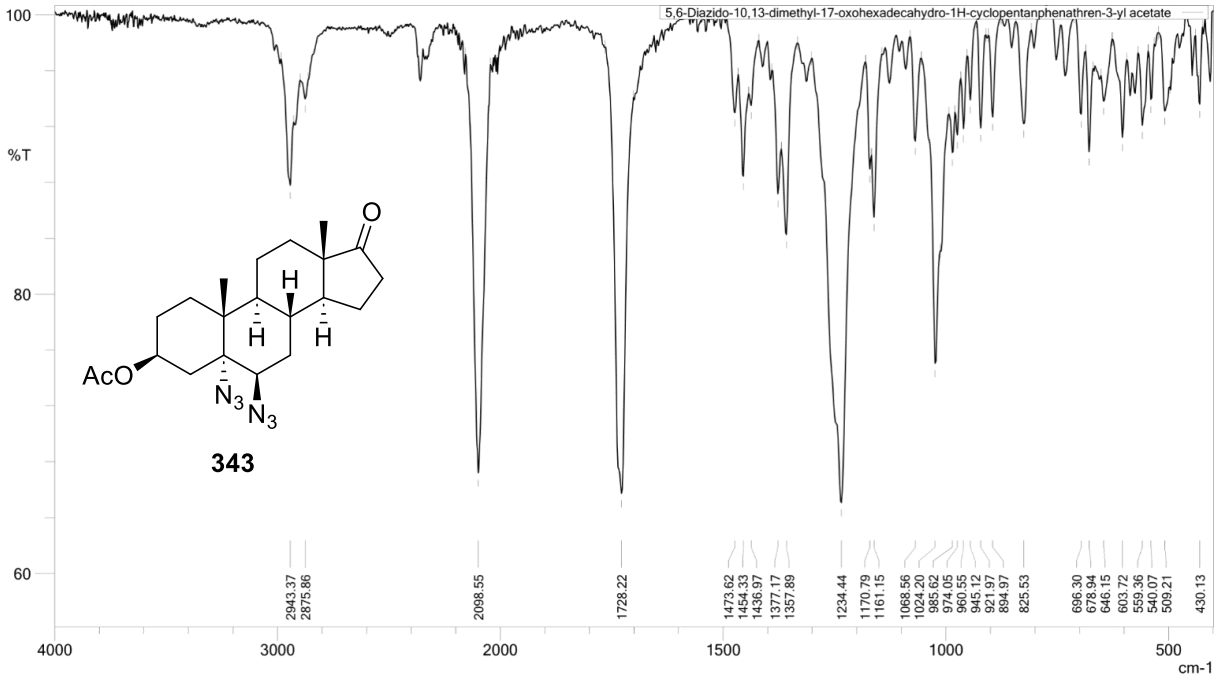


(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-5,6-Diazido-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (343)

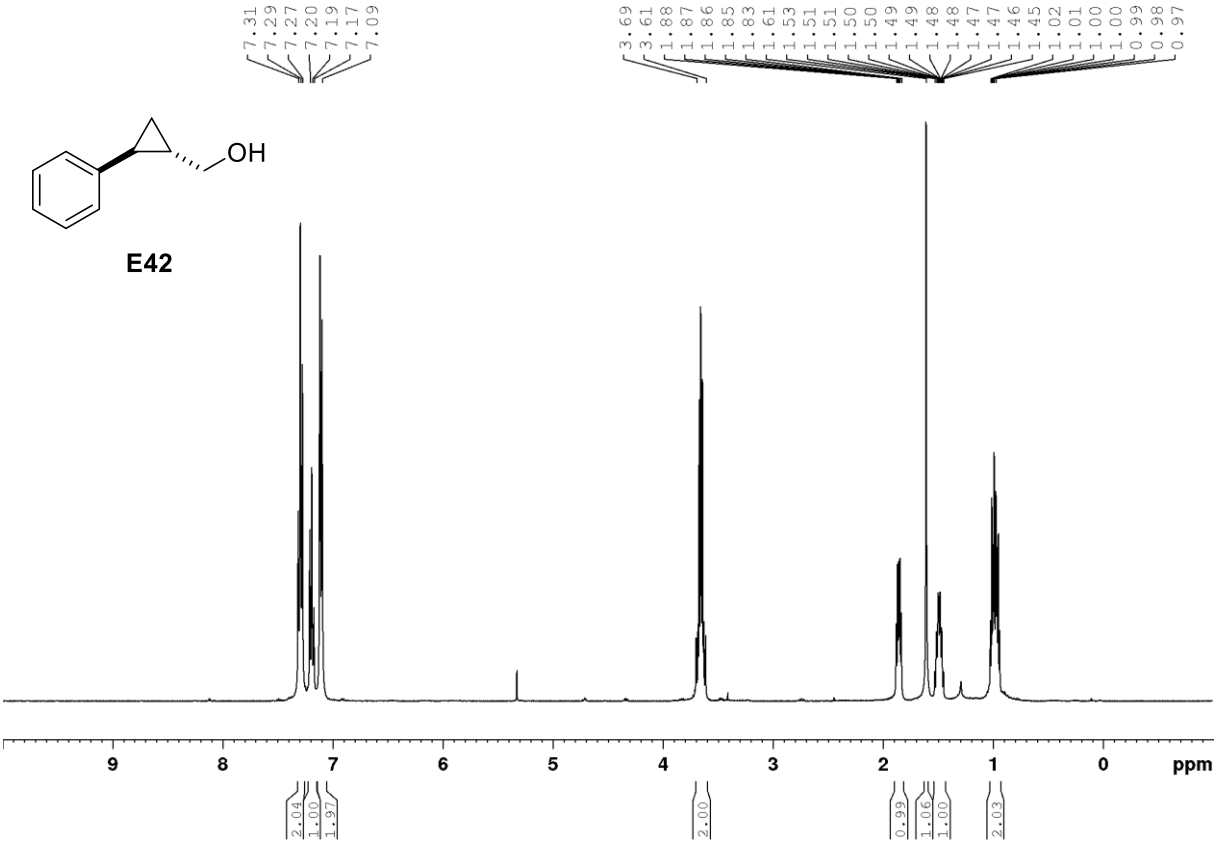


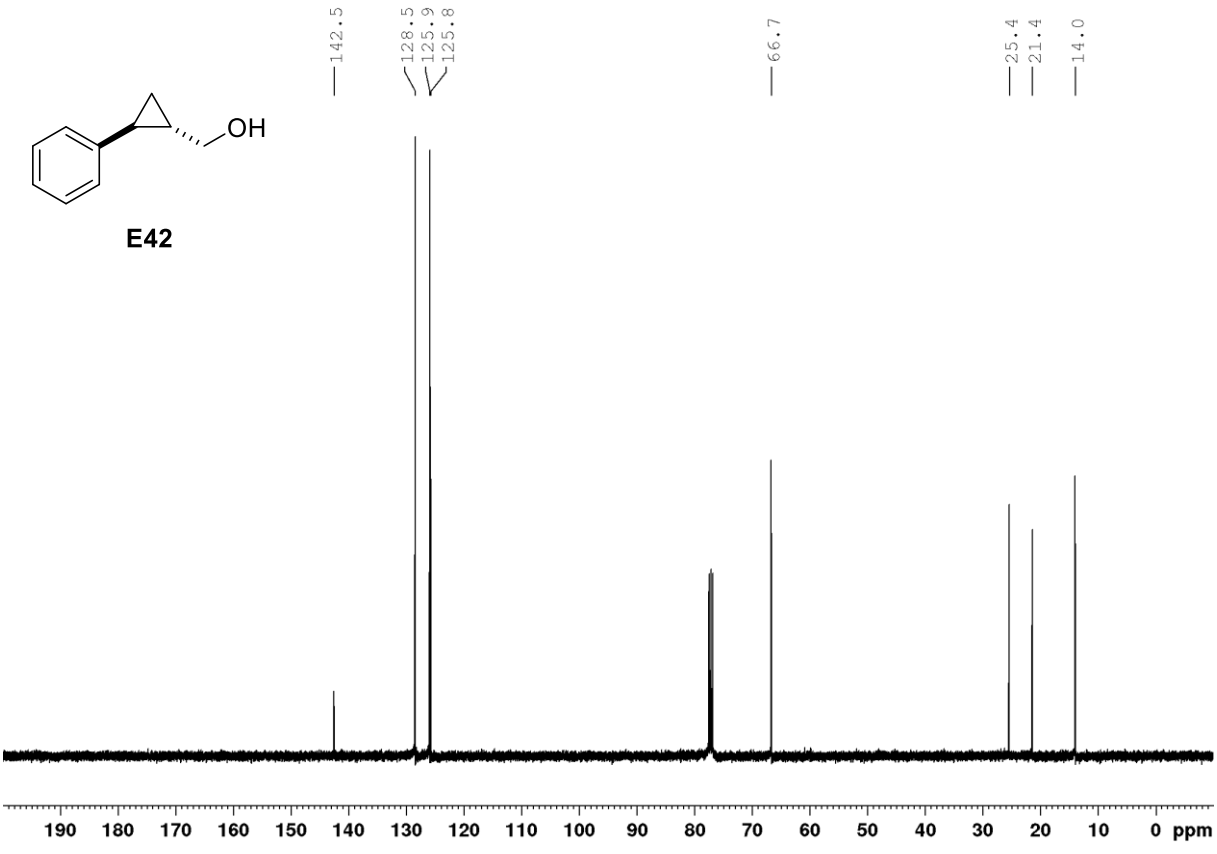
343


220.4
170.6
69.8
69.7
63.0
50.6
47.9
45.6
38.7
35.8
33.3
32.5
31.4
30.7
30.5
26.4
21.8
21.4
20.3
17.0
14.0
O
H
H
H
AcO
N3
N3
343
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

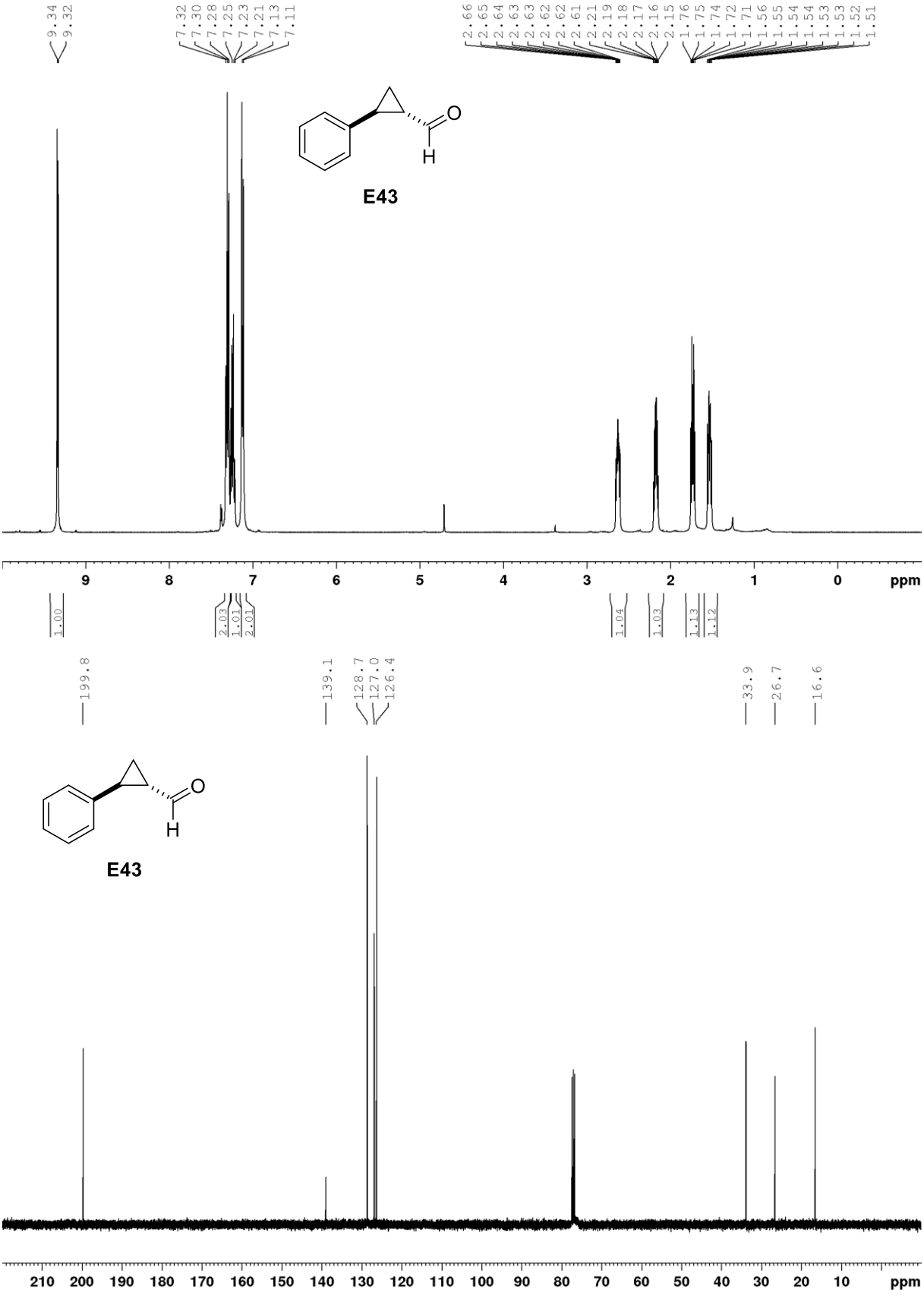

5,6-Diazido-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopentanphenathren-3-yl acetate
100
%T
80
60
O
H
H
H
AcO
N3
N3
343
2943.37
2875.86
2098.55
1728.22
1473.62
1454.33
1436.97
1377.17
1357.89
1234.44
1170.79
1161.15
1068.56
1024.20
985.62
974.05
960.55
945.12
921.97
894.97
825.53
696.30
678.94
646.15
603.72
559.36
540.07
509.21
430.13
4000
3000
2000
1500
1000
500
cm-1

(±)-((1*S*,2*S*)-2-Phenylcyclopropyl)methanol (E42)

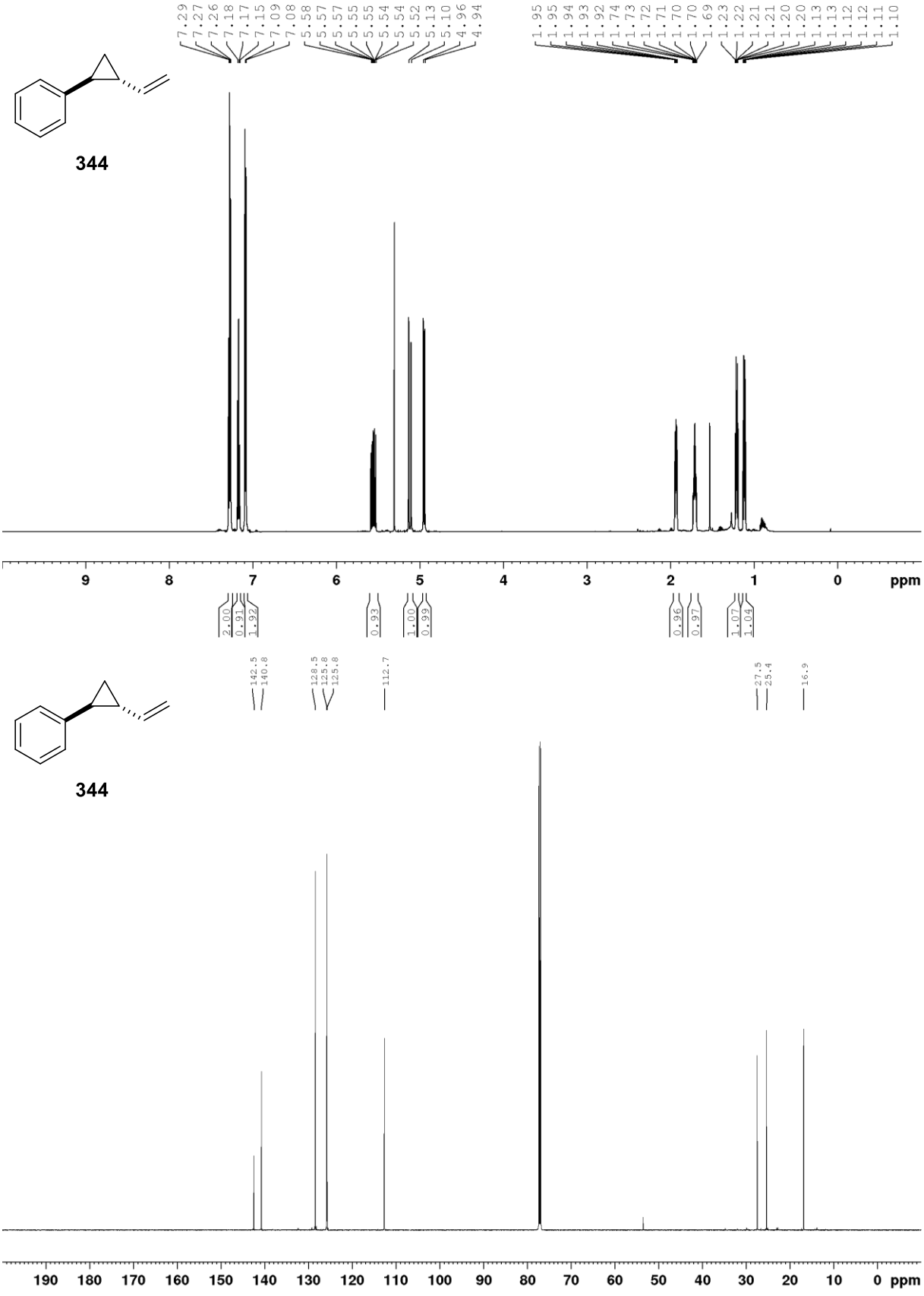




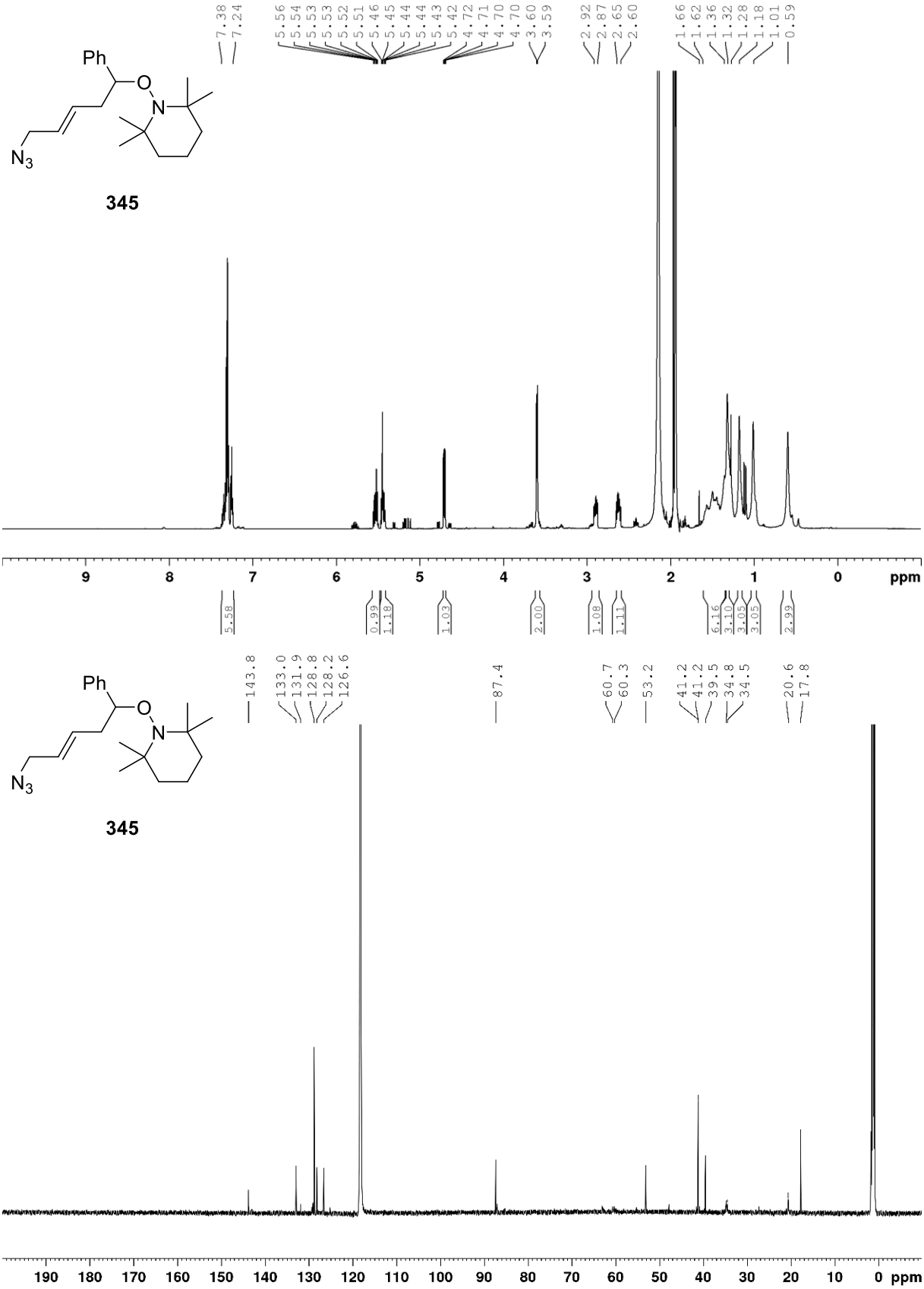
(±)-(1*S*,2*S*)-2-Phenylcyclopropane-1-carbaldehyde (E43)



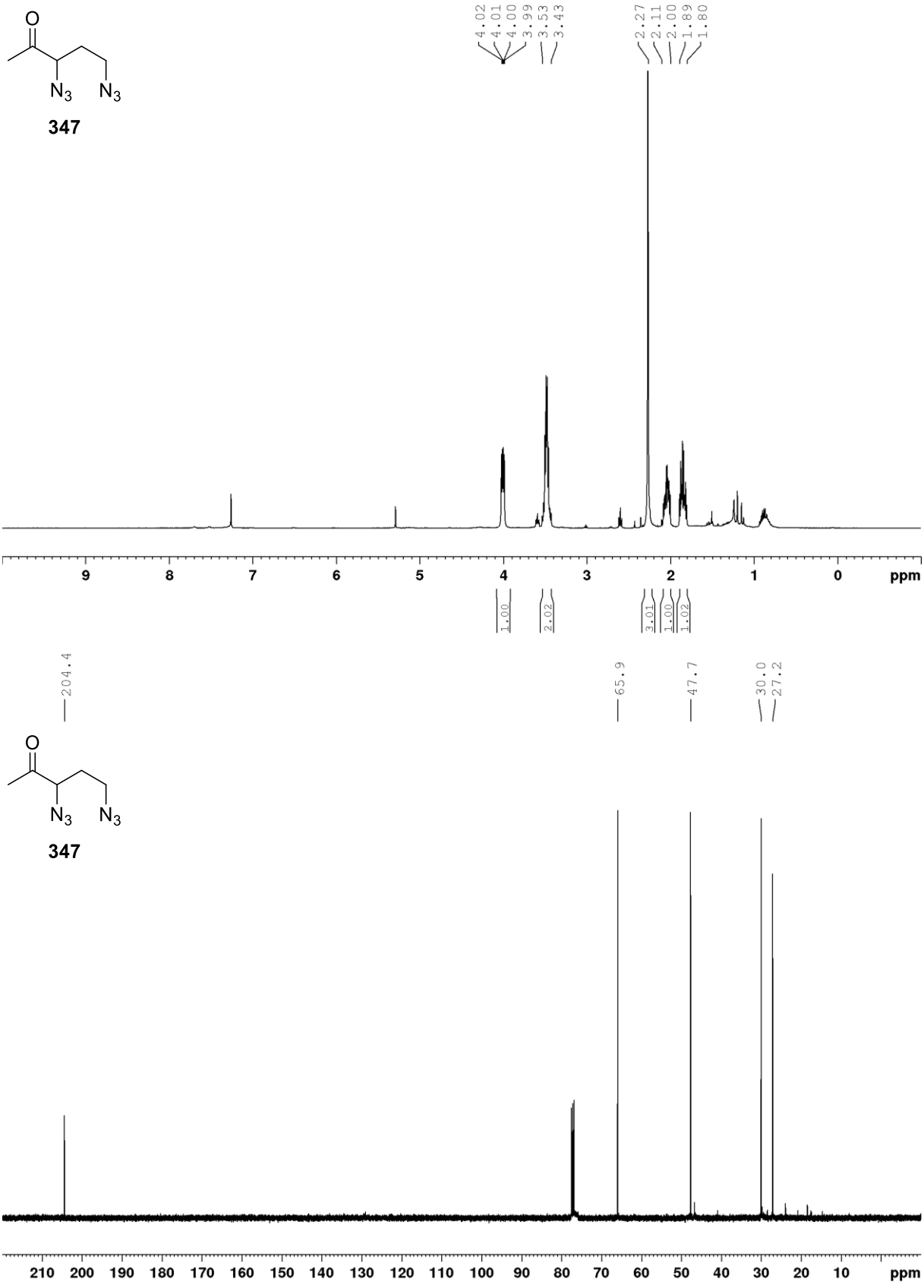
(±)-((1*S*,2*R*)-2-Vinylcyclopropyl)benzene (344)



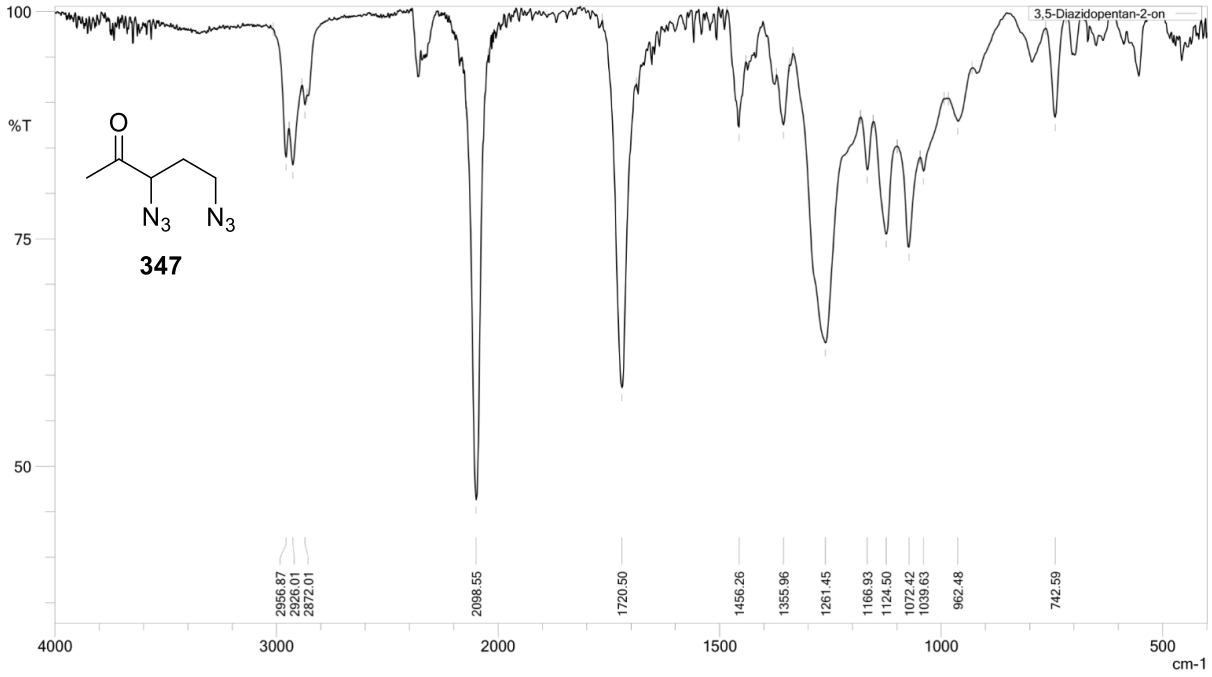
(*E*)-1-((5-Azido-1-phenylpent-3-en-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (345)



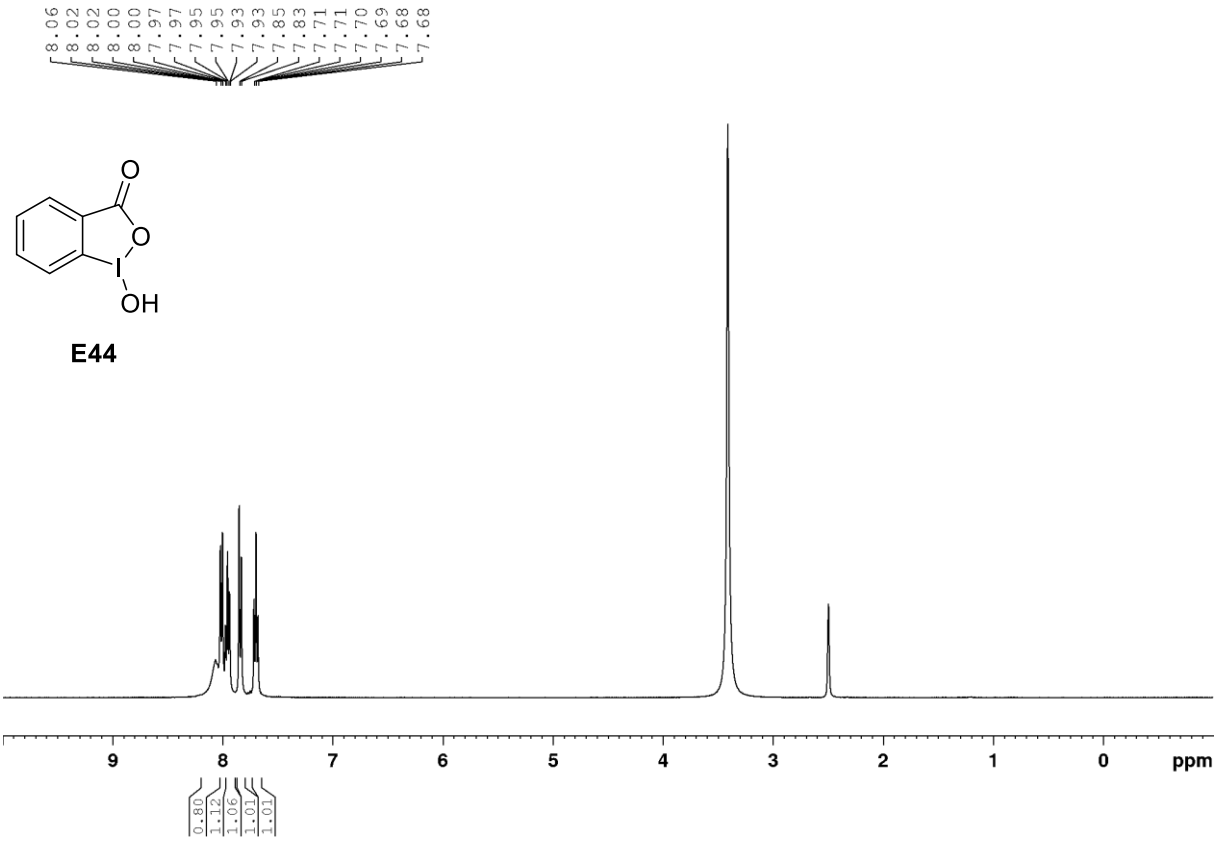
3,5-Diazidopentan-2-one (347)

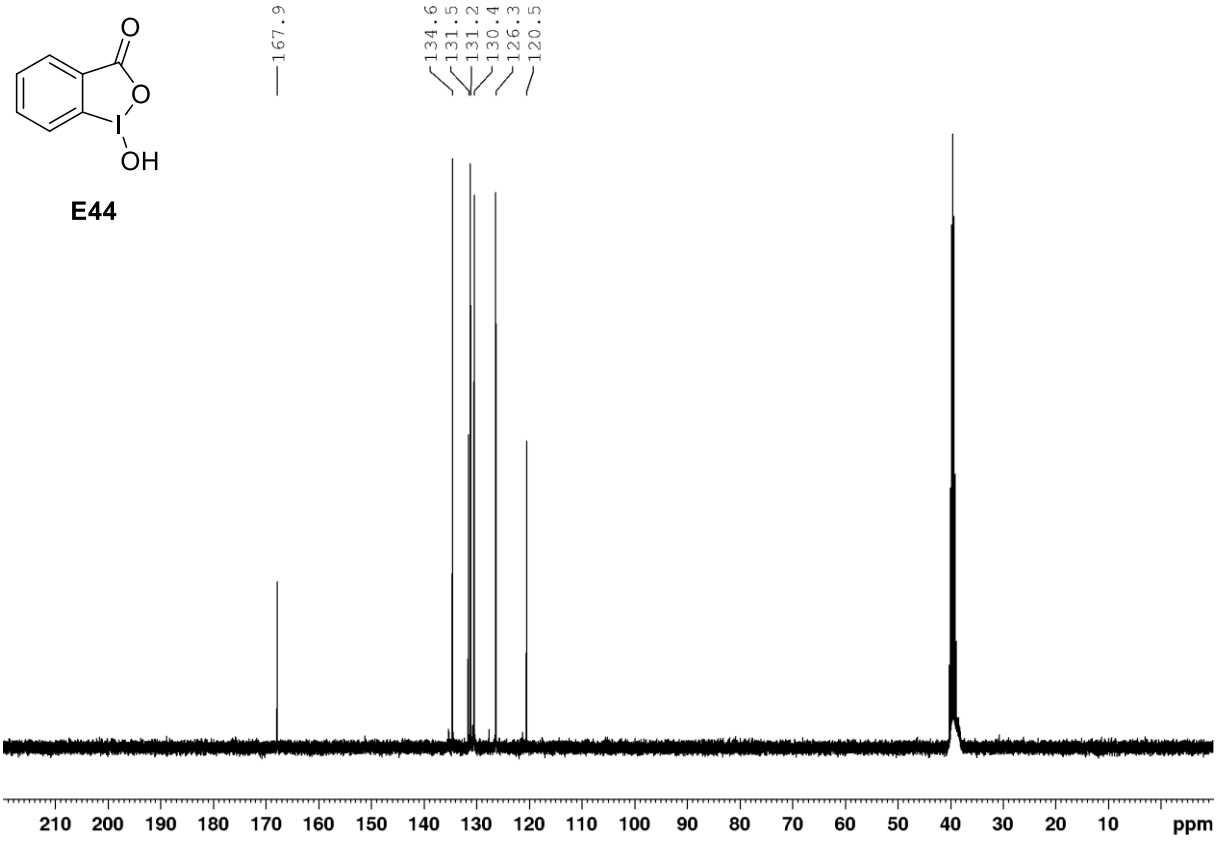


347



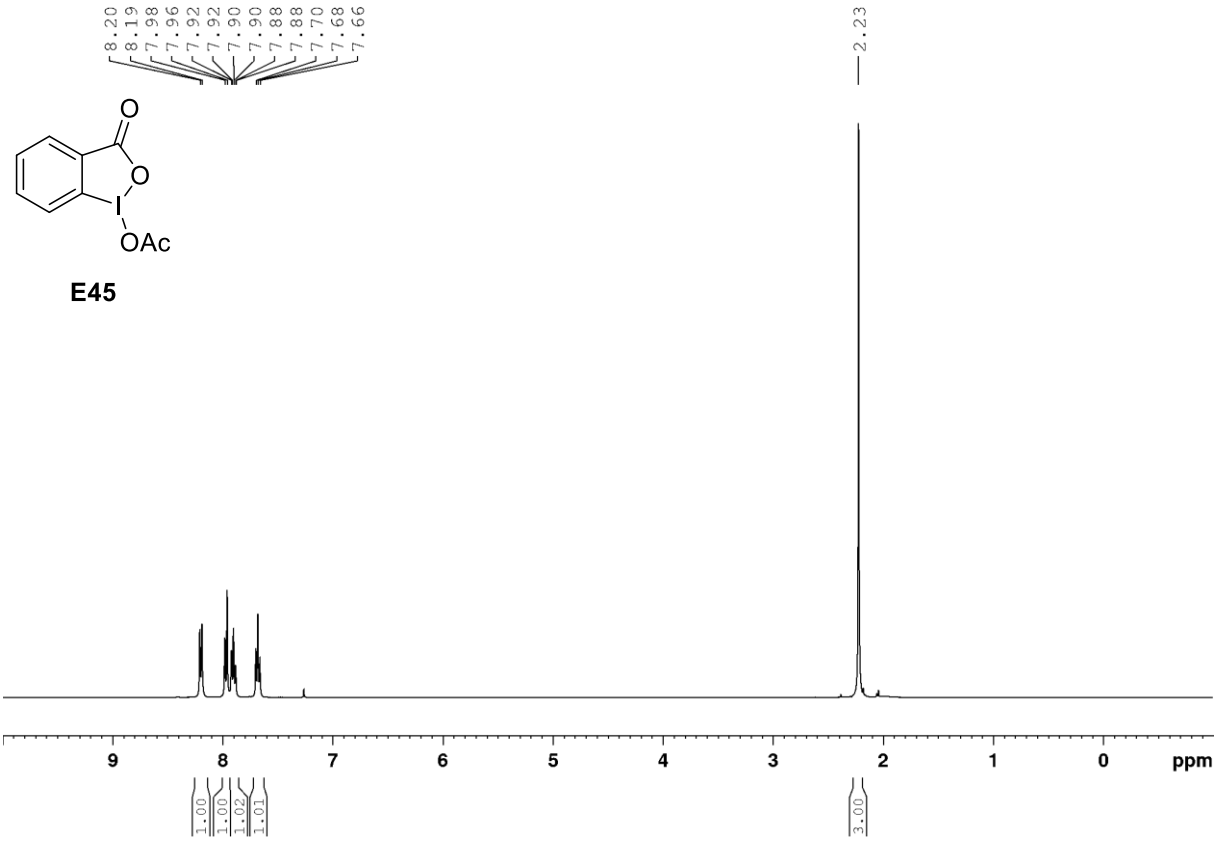
1-Hydroxy-1λ^3-benzo[d][1,2]iodaoxol-3(1*H*)-one (E44)



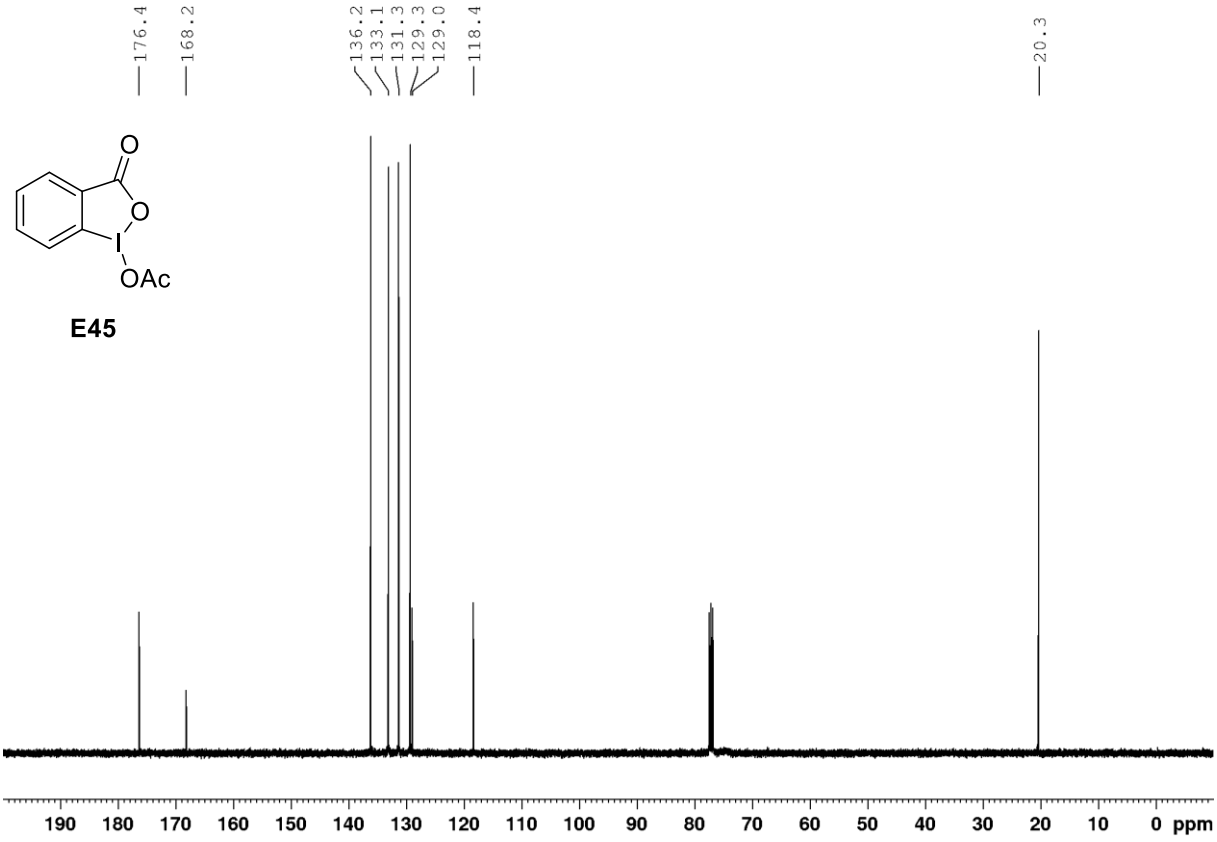


E44

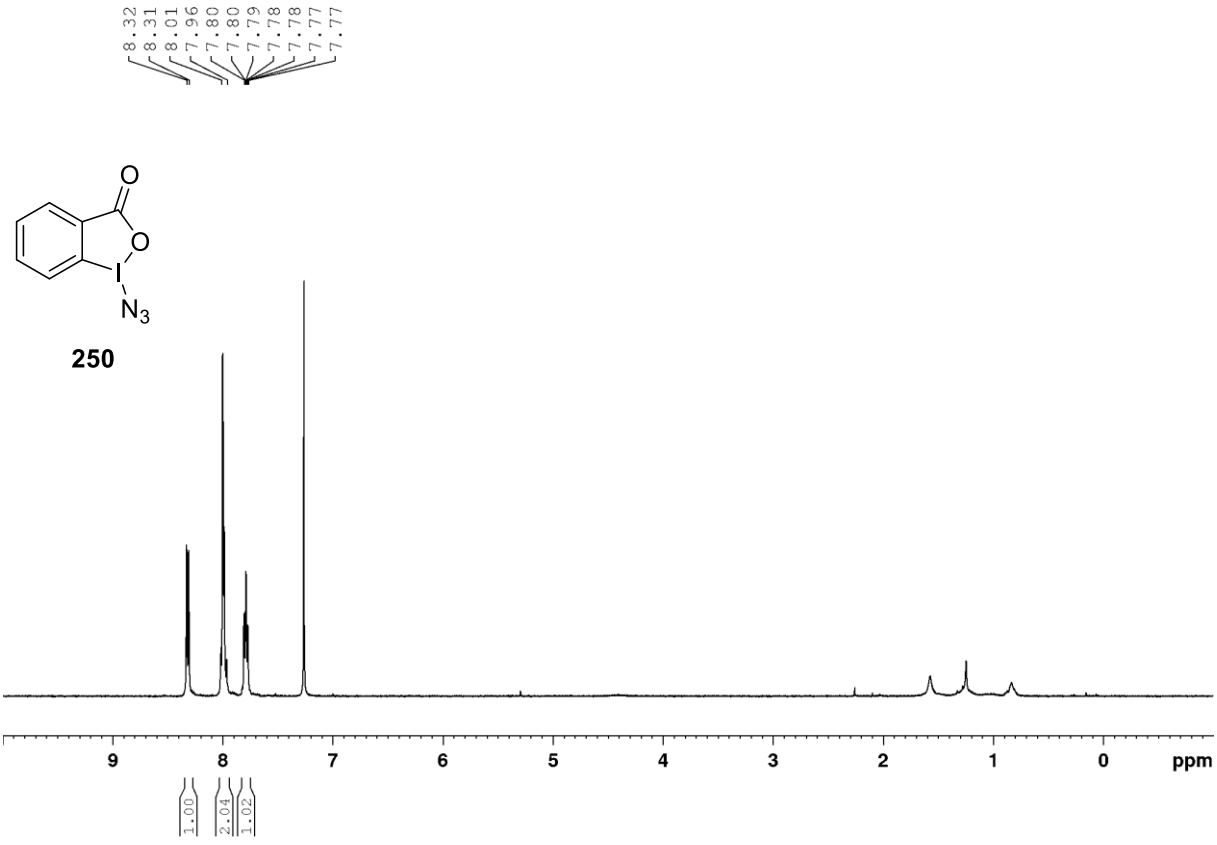
3-Oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (E45)

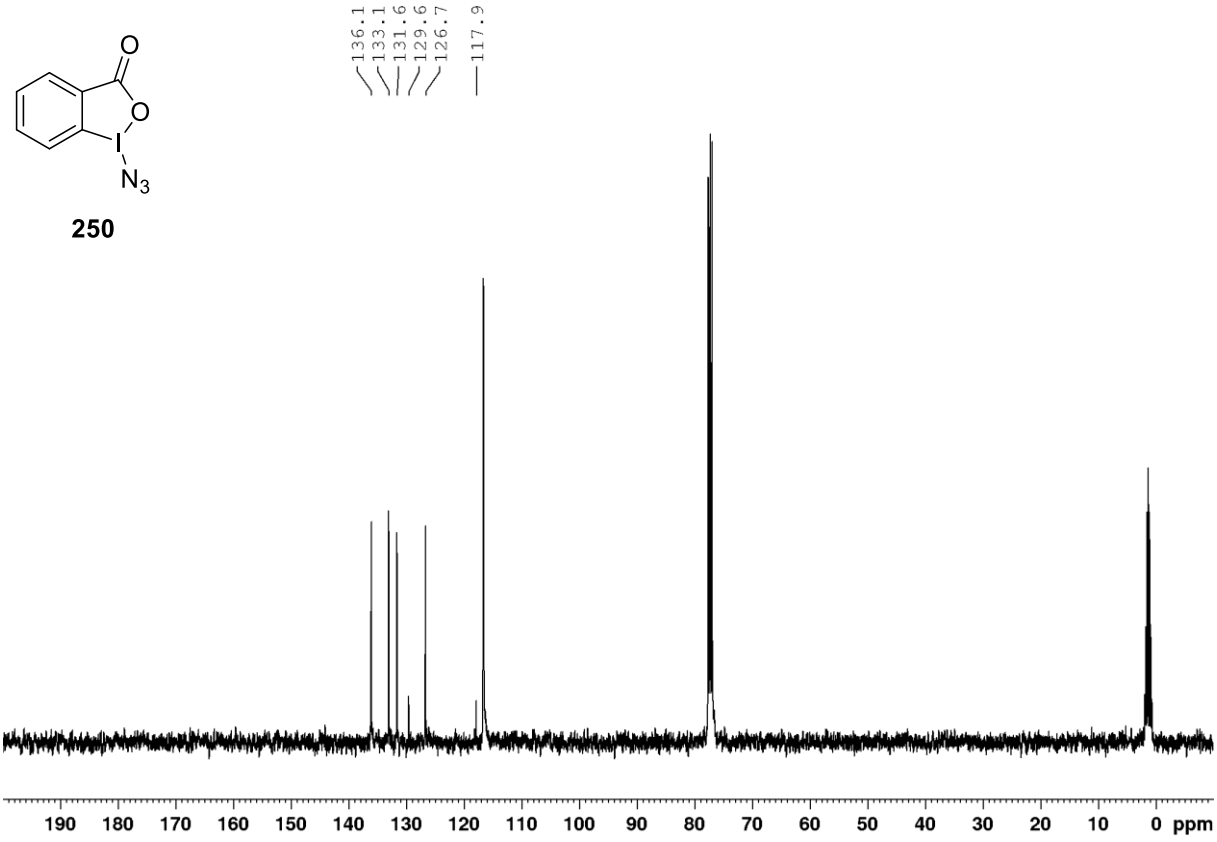


E45



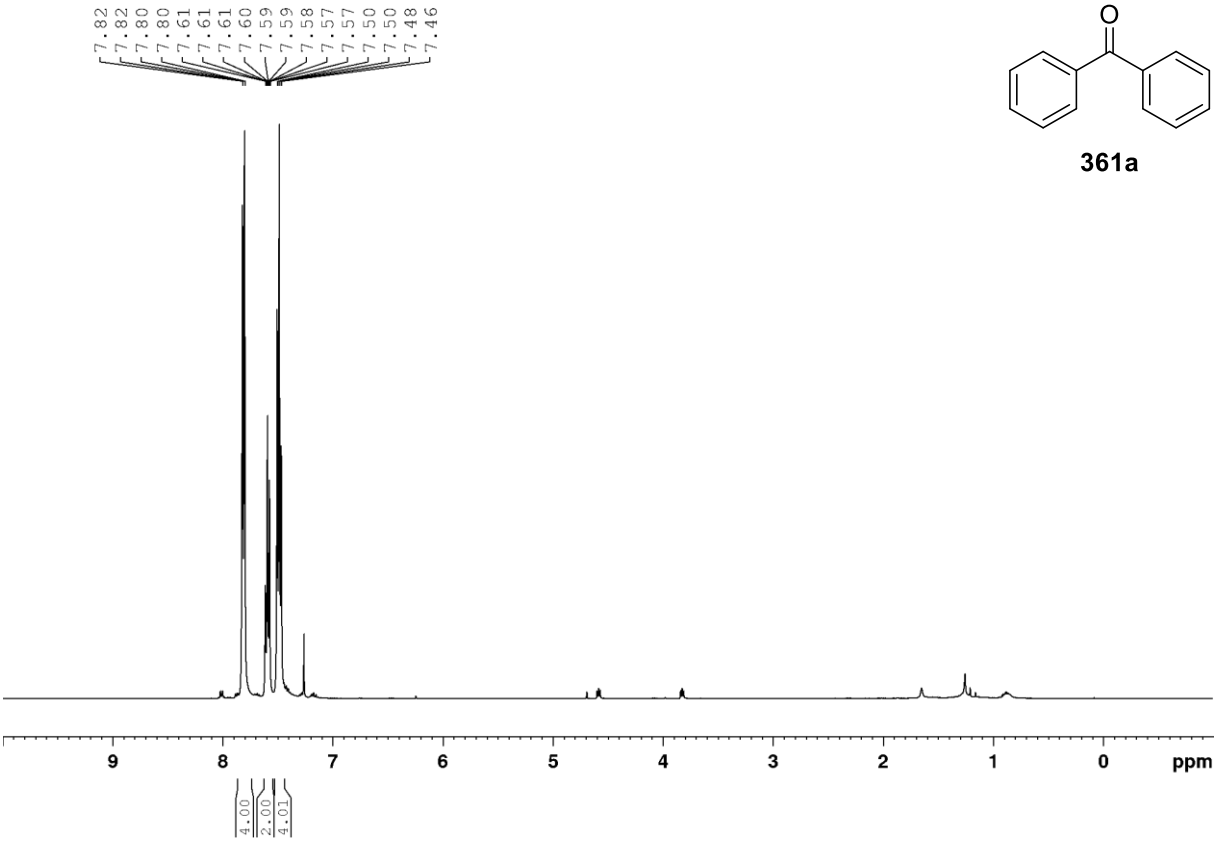
1-Azido-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (ZHDANKIN's reagent, 250)



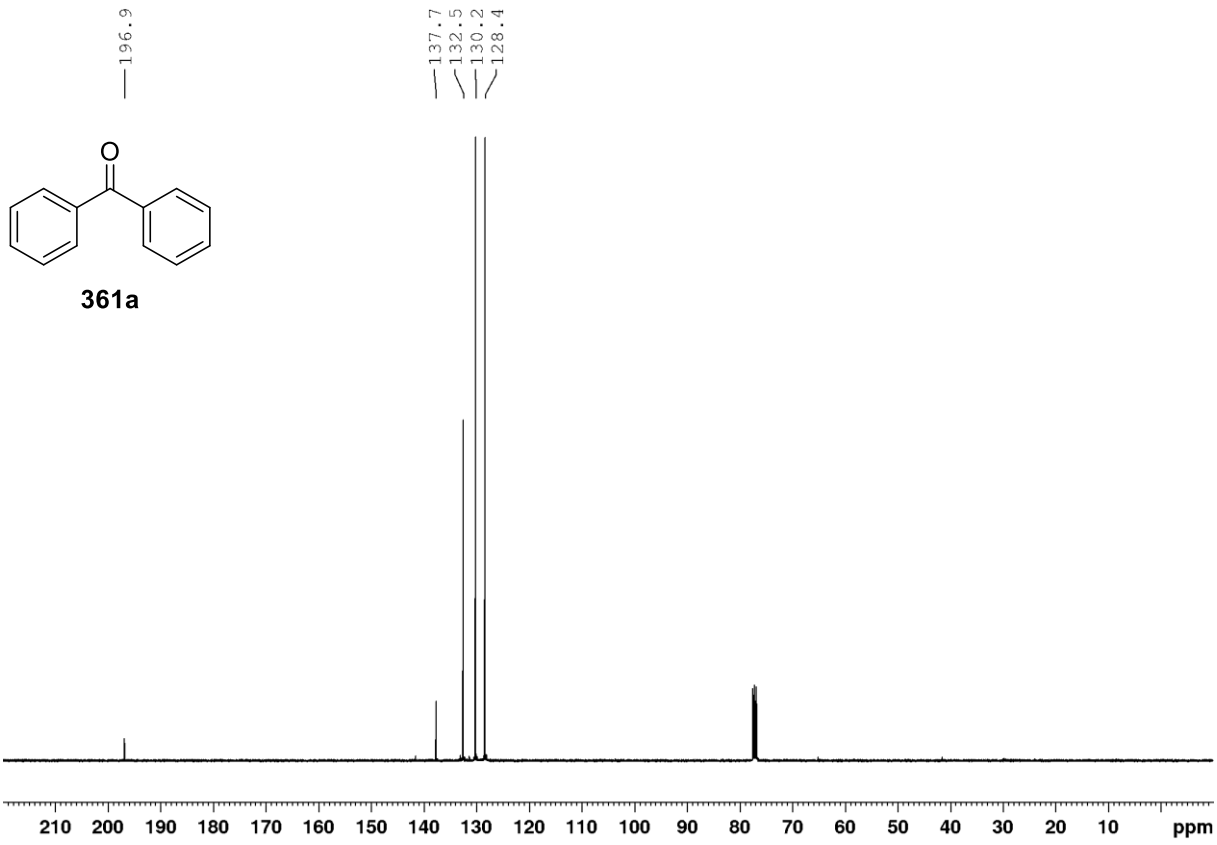


250

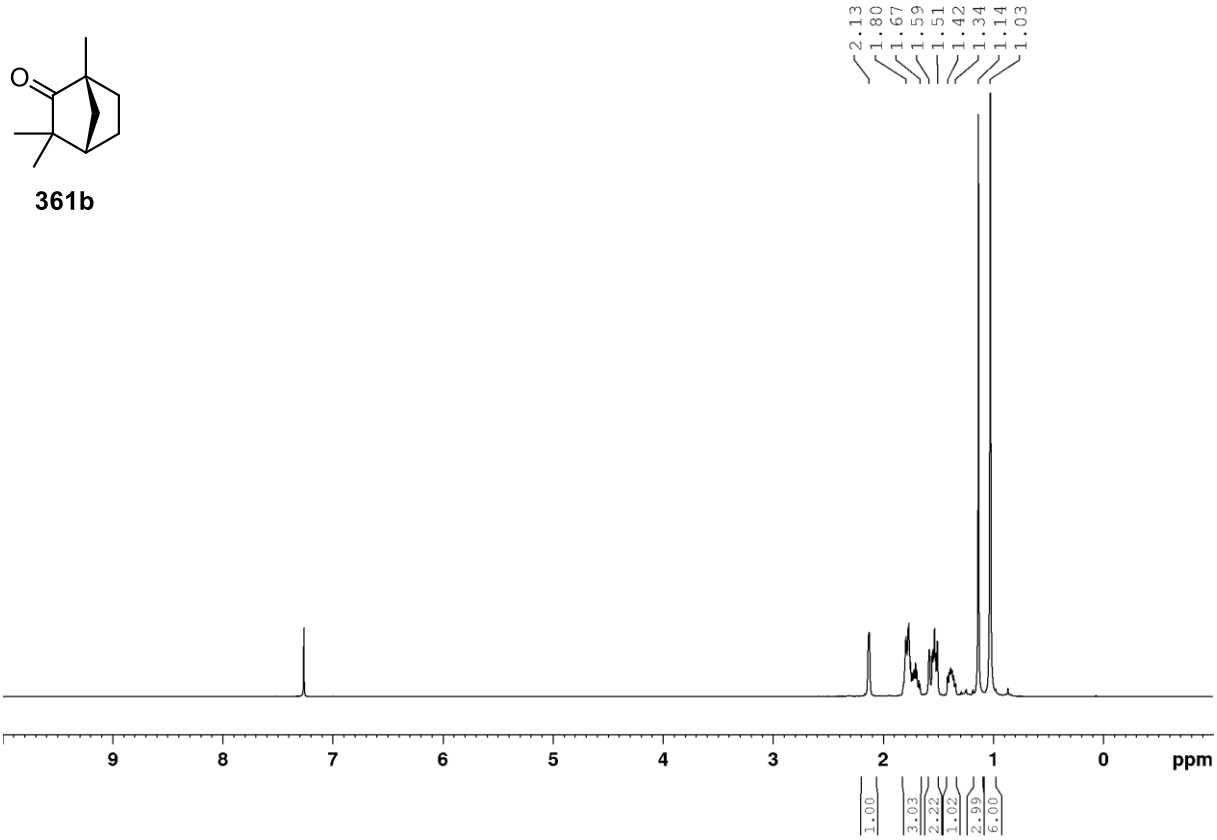
Benzophenone (361a)

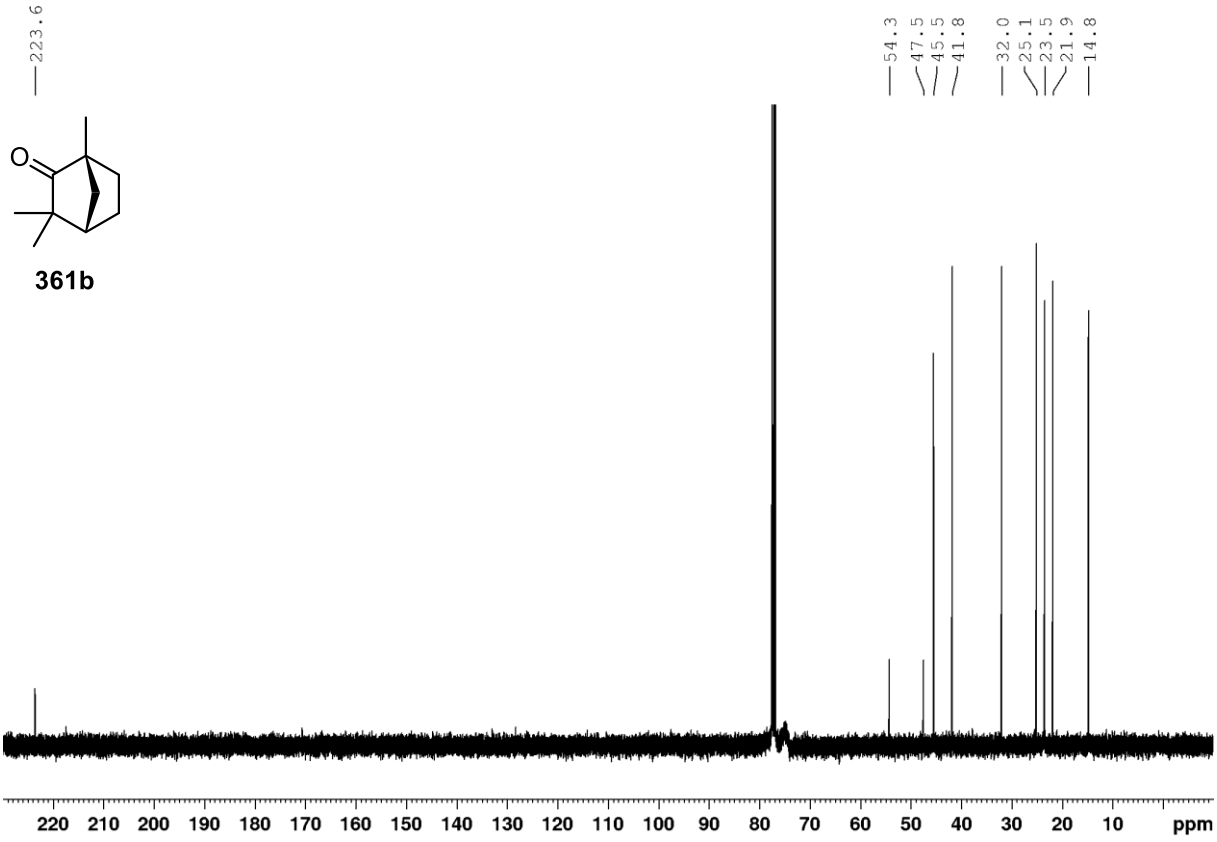


361a



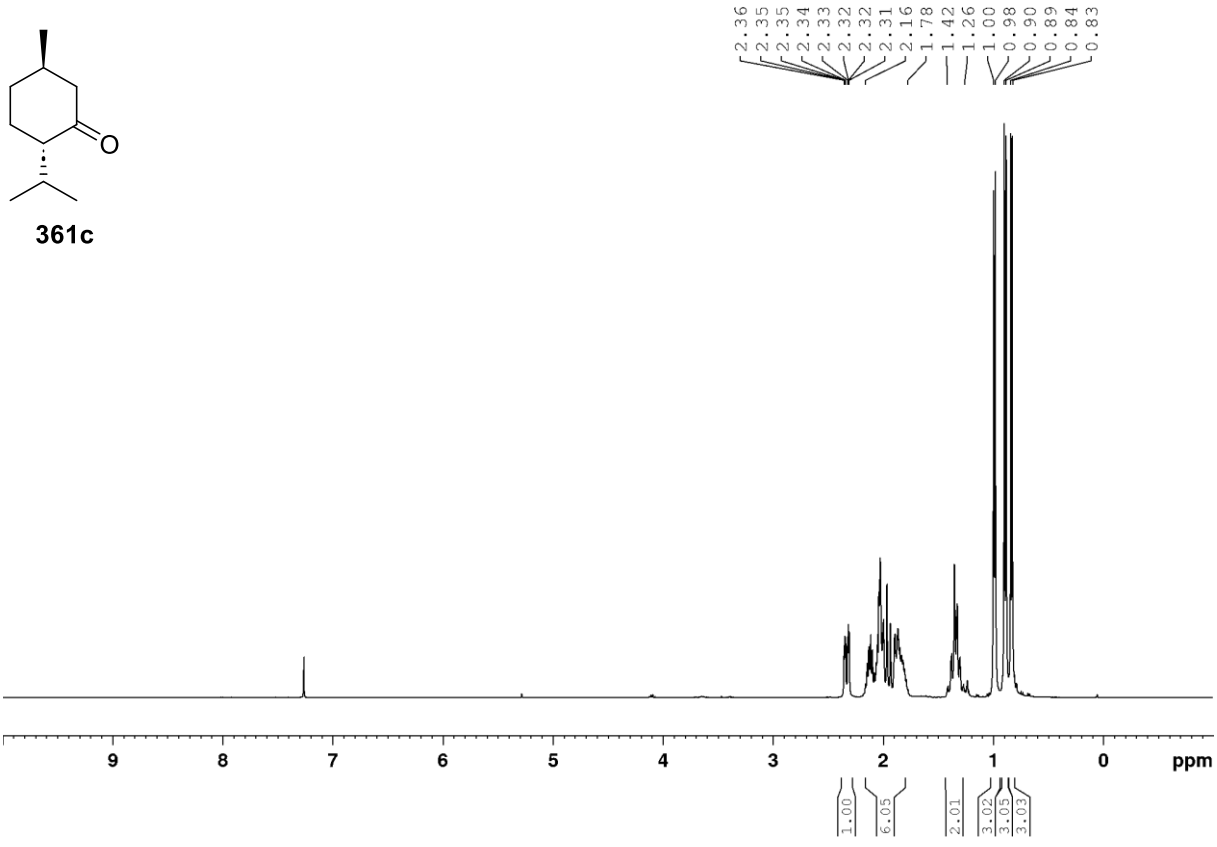
(*1R*,4*S*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one (361b)



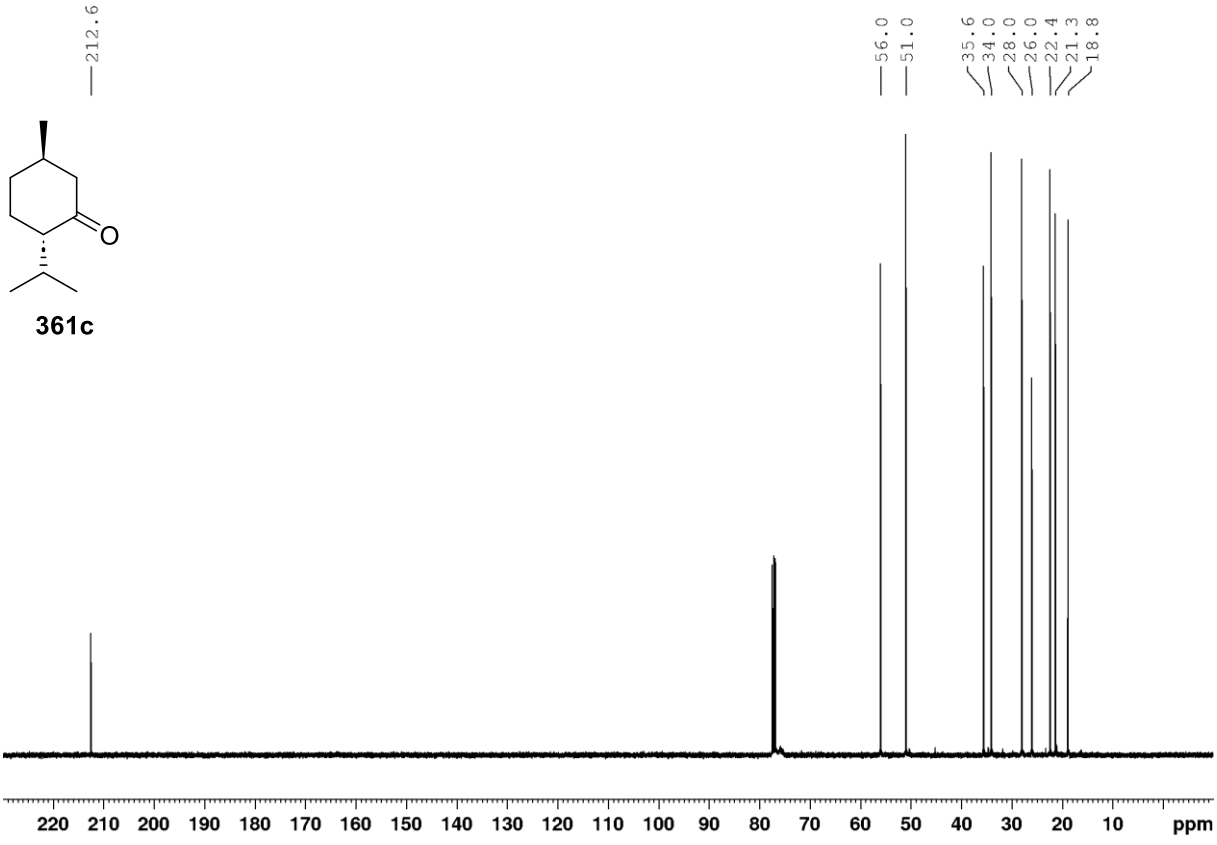


361b

(2*S*,5*R*)-2-Isopropyl-5-methylcyclohexan-1-one (361c)

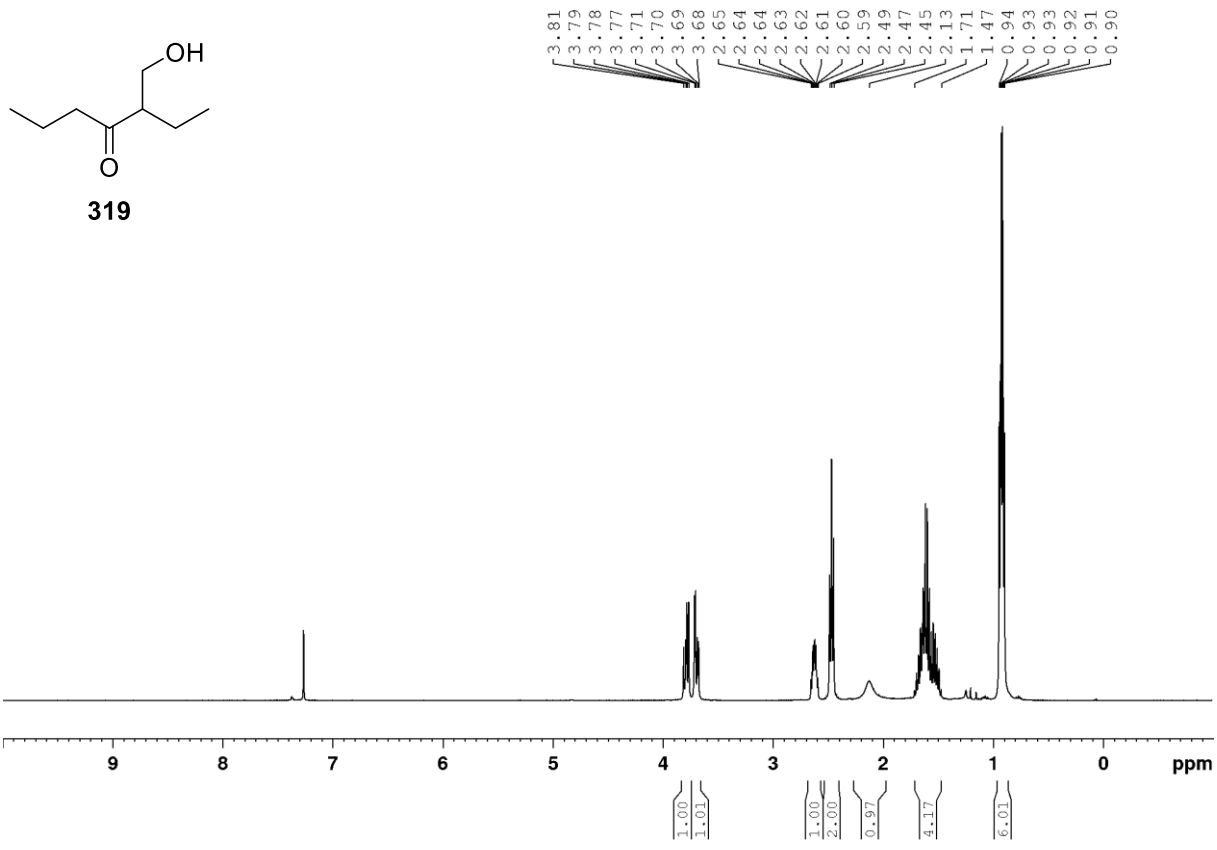


361c

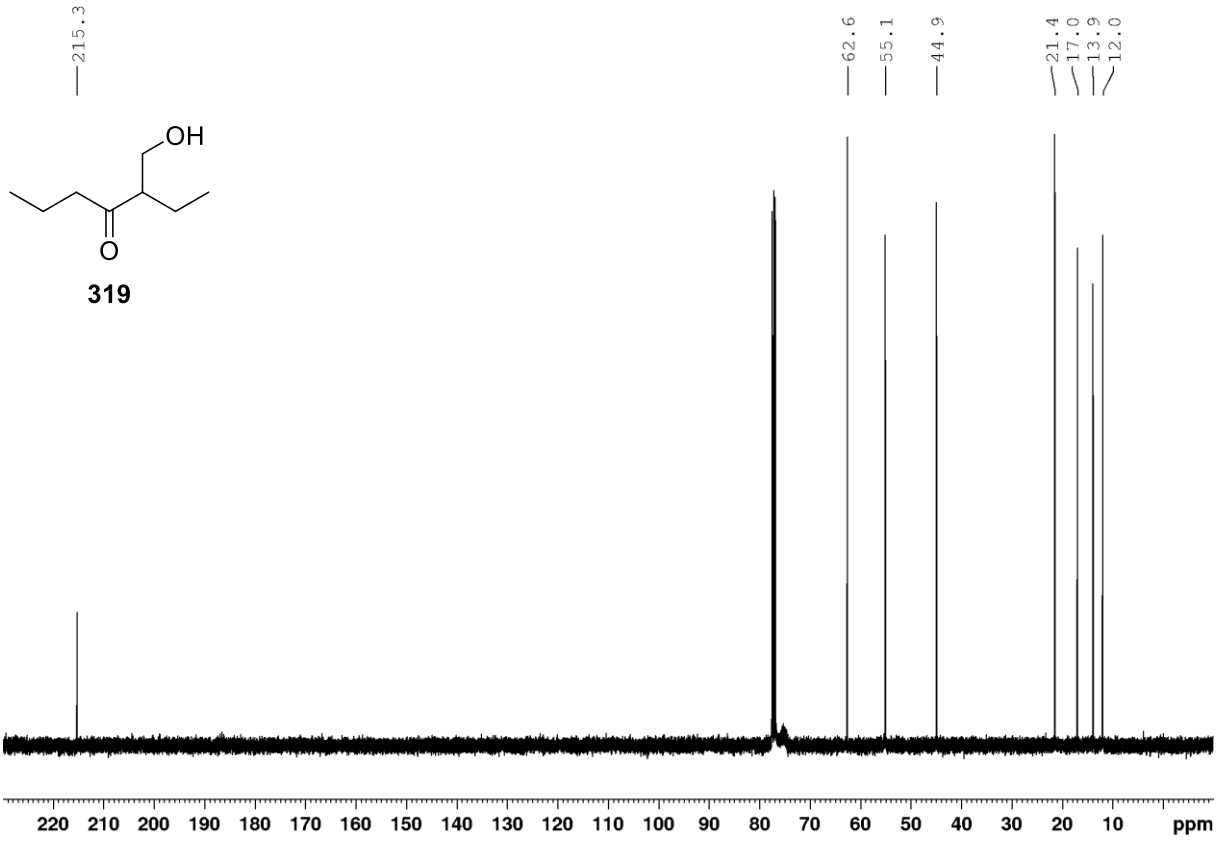


361c

3-(Hydroxymethyl)heptan-4-one (319)

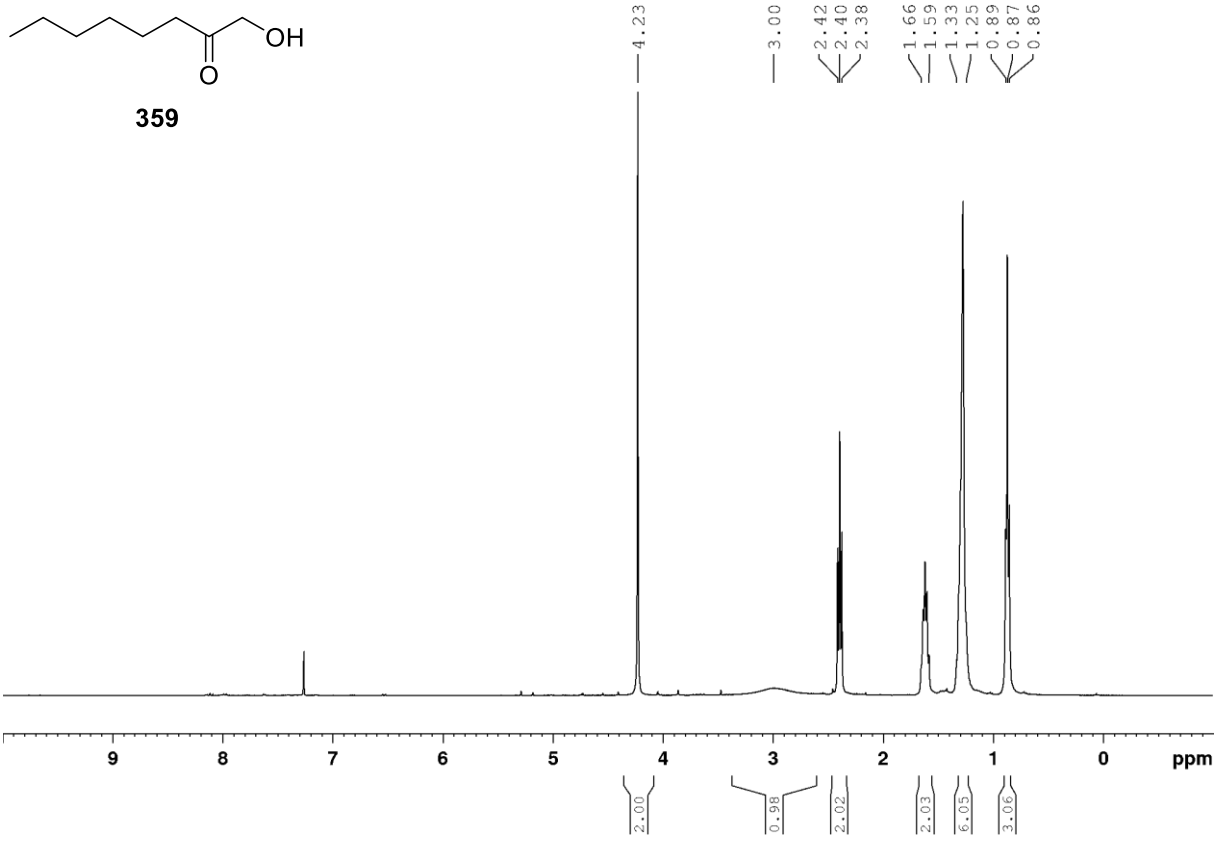


319

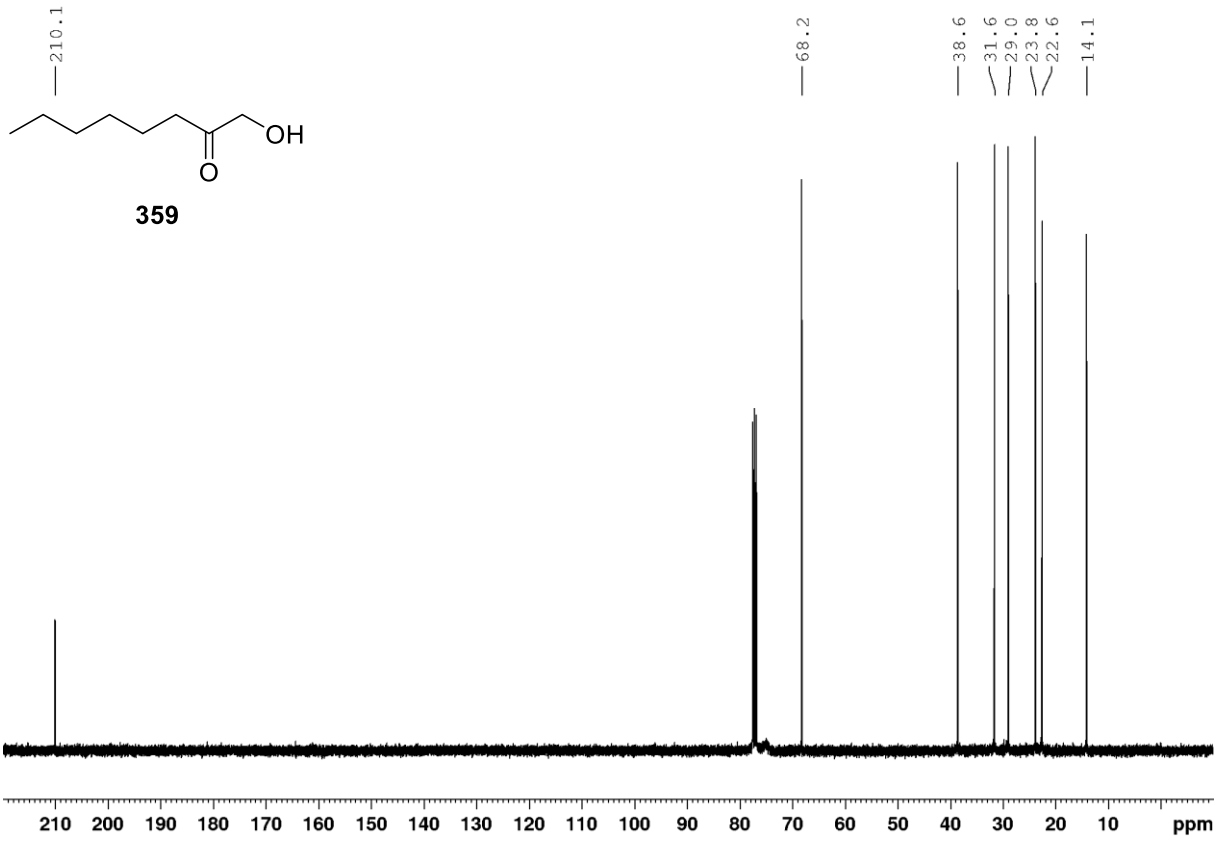


319

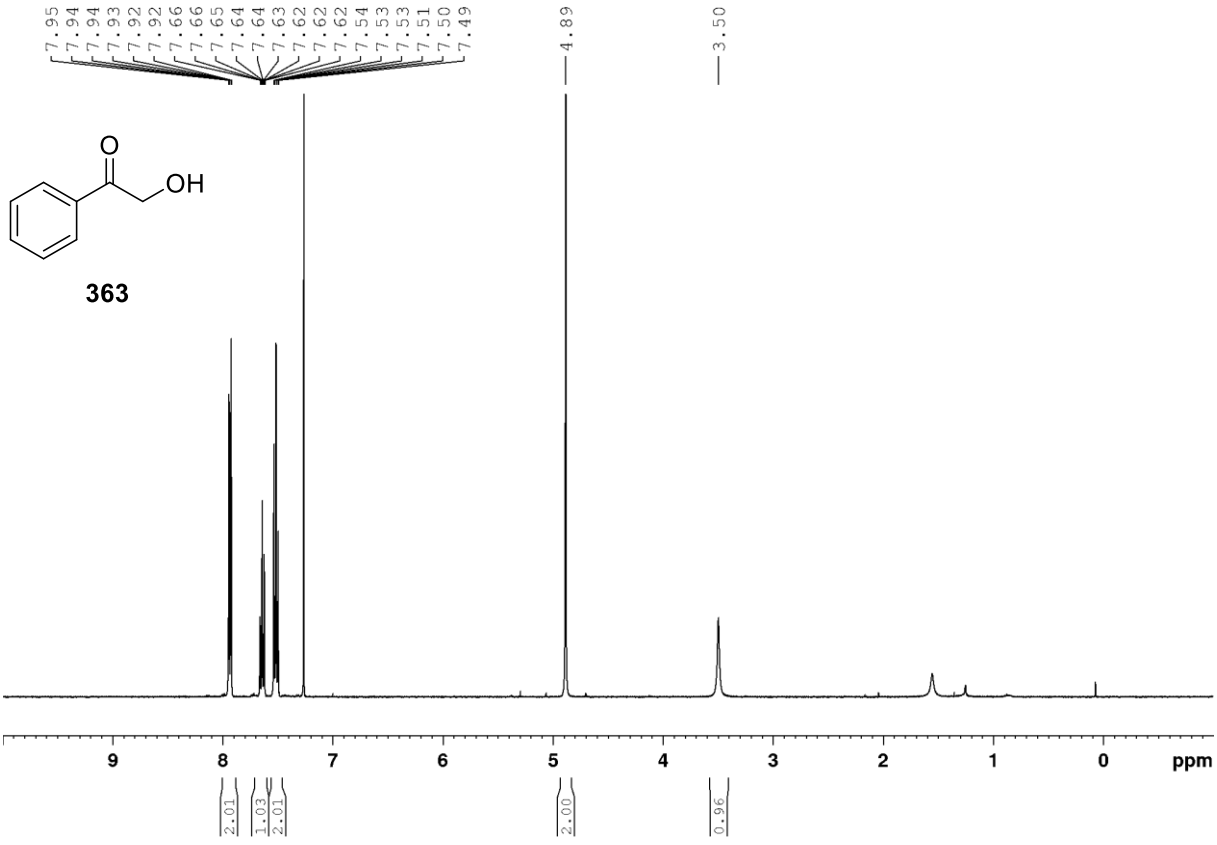
1-Hydroxyoctan-2-one (359)

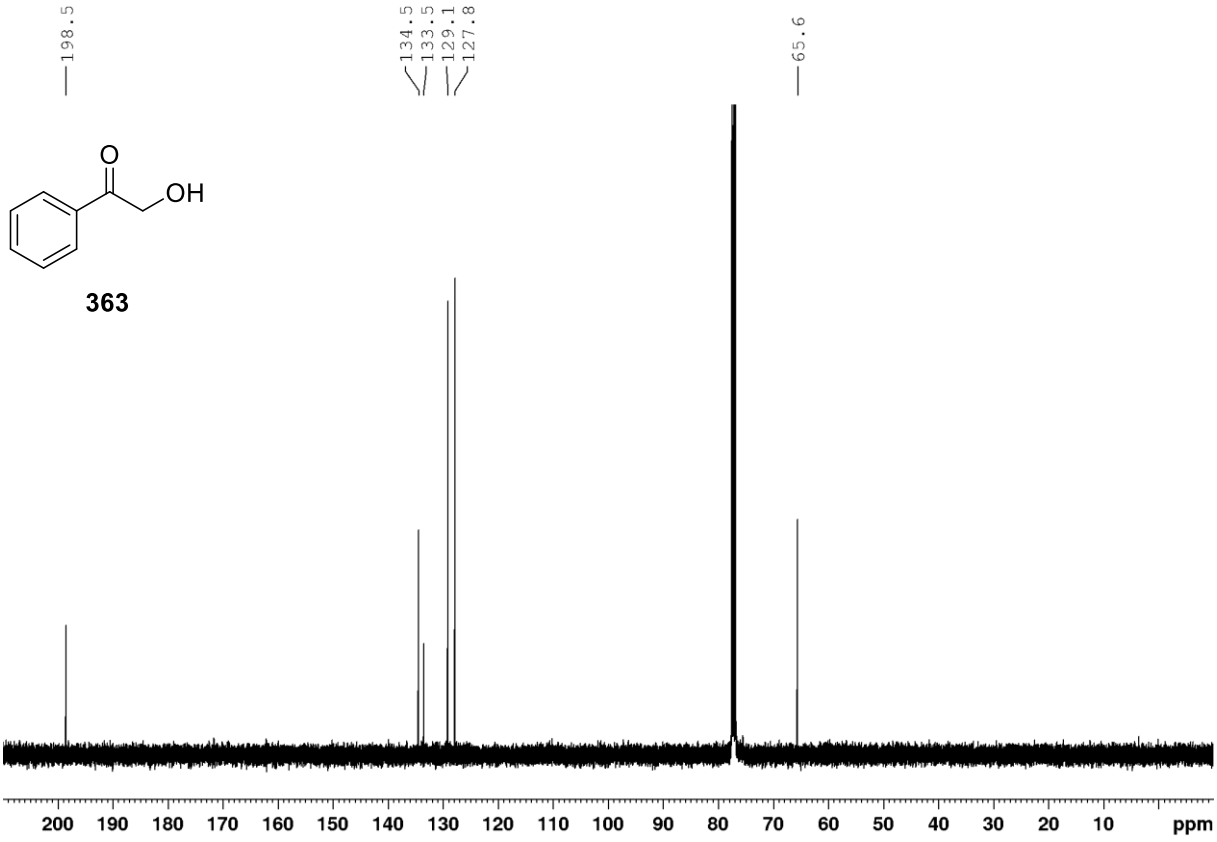


359



2-Hydroxy-1-phenylethan-1-one (363)




198.5
134.5
133.5
129.1
127.8
65.6
O
OH
363
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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Lebenslauf und Publikationsliste

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Name	Göran Schulz
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Staatsangehörigkeit	Deutsch

Akademischer Werdegang

Ab Juni 2019	Promotionsstudium, Leibniz Universität Hannover, "Synthesis of a Library of Antiviral Silvestrol Derivatives and Development of Novel Methodologies in the Field of Radical Chemistry" (Prof. A. Kirschning)
August 2017 – Januar 2018	ERASMUS+ Programm an der Stockholms universitet (Schweden) "Synthesis, Purification and Reactivity of Allenylboronic Acids" (Prof. K. J. Szabó)
Oktober 2016 – April 2019	Masterstudium Wirk- und Naturstoffchemie, Leibniz Universität Hannover Masterarbeit "Transition-metal-mediated Radical Deformylation of Aldehydes using various TEMPO derivatives" (Prof. A. Kirschning)
Oktober 2013 – Oktober 2016	Bachelorstudium Chemie, Leibniz Universität Hannover Bachelorarbeit „Zur Synthese von Indatralin und Studien zur asymmetrischen bisvinylogen Mukaiyama Aldol Reaktion" (Prof. M. Kalesse)

Preise und Auszeichnungen

September 2021	Lindemann-Stipendium für Promovierende auf dem technisch-naturwissenschaftlichen Gebiet (Dr. Heinz Lindemann Stiftung)

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[1] J. Zhao*, S. J. T. Jonker*, D. N. Meyer, G. Schulz, C. D. Tran, L. Eriksson, K. J. Szabó, *Chem. Sci.* **2018**, *9*, 3305-3312.

Copper-catalyzed synthesis of allenylboronic acids. Access to sterically encumbered homopropargylic alcohols and amines by propargylboration

[2] S. J. T. Jonker*, C. Diner*, G. Schulz, H. Iwamoto, L. Eriksson, K. J. Szabó, *Chem. Commun.* **2018**, *54*, 12852-12855.

Catalytic asymmetric propargyl- and allylboration of hydrazonoesters: a metal-free approach to sterically encumbered chiral α-amino acid derivatives

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[4] G. Schulz*, A. Kirschning, *Org. Biomol. Chem.* **2021**, *19*, 273-278.

Metal free decarboxylative aminoxylation of carboxylic acids using a biphasic solvent system

[5] G. Schulz*, C. Victoria*, A. Kirschning., E. Steinmann, *Nat. Prod. Rep.* **2021**, *38*, 18-23.

Rocaglamide and silvestrol: A long story from anti-tumor to anti-coronavirus compounds

[6] A. Eggert*, C. Etling*, L. Millbrodt, G. Schulz, M. Kalesse, *Org. Lett.* **2021**, *22*, 8722-8726.

Oxazaborolidinone-Mediated Asymmetric Bisvinylogous Mukaiyama Aldol Reaction

[7] G. Schulz*, V. George*, D. Taser*, A. Kirschning, *J. Org. Chem.* **2023**, *88*, 3781-3786.

Taming Bromine Azide for Use in Organic Solvents—Radical Bromoazidations and Alcohol Oxidations

Konferenzen/Posterbeiträge

[1] European Symposium on Organic Chemistry (ESOC), **2019**, Wien/Österreich

Transition-Metal-Mediated Radical Deformylation of Aldehydes using various Aminoxyl Radicals

[2] 34. Irseer Naturstofftage, Online Konferenz, **2022**, Irsee/Deutschland

Combating SARS-CoV 2: Synthesis of a Silvestrol and Rocaglamide Library with Antiviral Properties

[3] 22nd Tetrahedron Symposium, **2022**, Lissabon/Portugal

Synthesis of Rocaglamide and Silvestrol Derivatives with Optimized Antiviral Properties